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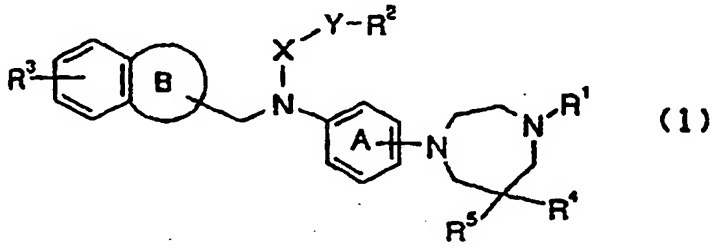
添付公開書類
国際調査報告書

(54)Title: **NOVEL HEXAHYDRO-1,4-DIAZEPINE DERIVATIVES OR SALTS THEREOF**

(54)発明の名称 新規なヘキサヒドロ－1,4－ジアゼピン誘導体又はその塩



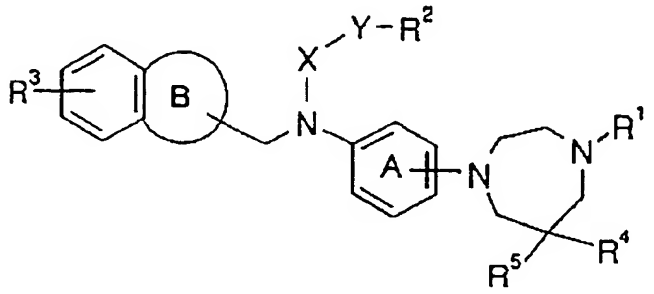
(1)

(57) Abstract

Hexahydro-1,4-diazepine derivatives represented by general formula (1); pharmaceutically acceptable salts thereof; and drugs containing the same as the active ingredient, such as activated blood coagulation factor X inhibitor, wherein A: phenylene, pyridylene, or the like; B: a 5- or 6-membered aryl or heteroaryl ring; X: -CO-, -CONH-, -CSNH-, SO_2-,-SO_2NH-, or the like; Y: a bond or alkylene; R^1: hydrogen, alkyl, -Y- (hetero)aryl, or the like; R^2: hydrogen, alkoxy, -COOH, or the like; R^3: amidino or a group capable of being converted into amidino; and R^4, R^5: each independently hydrogen or lower alkyl.

(57)要約

下記一般式（１）で示されるヘキサヒドロ－１，４－ジアゼピン誘導体、その製薬学的に許容される塩、及びそれらを有効成分とする医薬、殊に活性化血液凝固第Ｘ因子阻害剤に関する。



（１）

（但し、Ａ：フエニレン、ピリジレン基等、
Ｂ　：５員又は６員のアリール環又はヘテロアリール環、
Ｘ　：-CO-、-CONH-、-CSNH-、-SO2-、-SO2NH-等、
Ｙ　：結合又はアルキレン基、
Ｒ１：水素原子、アルキル、－Ｙ－（ヘテロ）アリール等、
Ｒ２：水素原子、アルコキシ、-COOH等、
Ｒ３：アミジノ基又はアミジノ基に転化されうる基
Ｒ４，Ｒ５：同一又は異なって、水素原子又は低級アルキル基を表す）

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明　細　書

新規なヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩

技術分野

本発明は、医薬、特に活性化血液凝固第Ｘ因子阻害剤として有用なヘキサヒドロ－１，４－ジアゼピン導体又はその塩に関する。

背景技術

近年、生活習慣の欧米化、人口の高齢化などに伴い、心筋梗塞、脳血栓症、末梢動脈血栓症をはじめとする血栓塞栓性疾患は年々増加し、その治療の社会的重要性はますます高まっている。

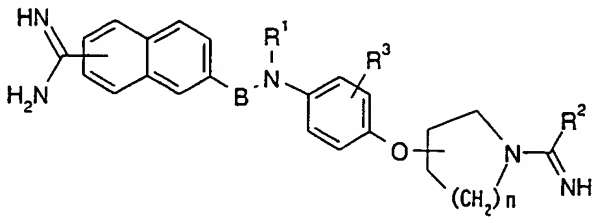
抗凝固療法は、線溶療法および抗血小板療法とともに血栓症の治療および予防における内科的治療法の一端を担っており（総合臨床 41：2141-2145,1989）、特に、血栓症の予防に用いられる抗凝固剤は長期投与に耐えうる安全性と確実かつ適切な抗凝固活性の発現が必須となる。

しかしながら、唯一の経口抗凝固剤として世界中に繁用されるワルファリンカリウムは、その作用機序に基づく特性から抗凝固能のコントロールが難しく（J. Clinical Pharmacology,32,196-209,1992/N.Eng.J.Med.,324(26),1865-1875,1991）、臨床的には非常に使用しづらい薬剤である。

ここで、トロンビンは、凝固の最終段階であるフィブリノーゲンのフィブリンへの転化を司り、血小板の活性化および凝集にも深く関与することが知られている。しかしながら、現在のところ、経口投与での bioavailability の低さ、安全性の問題から（Biomed.Biochim.Acta,44,1201-1210,1985）、経口投与可能なトロンビン阻害剤は上市されていない。

一方、活性化血液凝固第Ｘ因子は、外因系および内因系凝固カスケード反応の合流点に位置する Key Enzyme であり、本因子の阻害はトロンビン阻害よりも効率的でかつ、特異的に凝固系を阻害できる可能性がある（THROMBOSIS RESEARCH(19),339-349,1980）。

活性化血液凝固第Ｘ因子阻害作用を示す化合物としては、アミジノナフチルベンゼン誘導体又はその塩が知られており（特開平 5－208946 号/Thrombosis Haemostasis,71(3),314-319,1994/Thrombosis Haemostasis,72(3),393-396,1994）、また、WO96/16940 には、下記一般式で示されるアミジノナフチル誘導体又はその塩が開示されている。



〔式中、Ｂ：低級アルキレン基等、R^1：水素原子又は式－Ａ－Ｗ－R^4で示される基［Ａ：－ＣＯ－、－SO_2－等、Ｗ：単結合又は－NR^5－基（R^5：水素原子、－$CONH_3$基等）、R^4：置換されていてもよい低級アルキル基等］、R^2：低級アルキル基、R^3：水素原子、ハロゲン原子等、ｎ＝０又は１〕

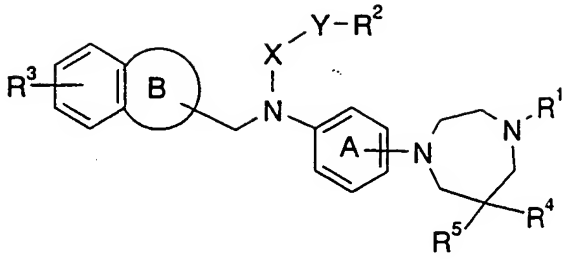
上述の通り、活性化血液凝固第Ｘ因子阻害剤は、抗凝固療法において、トロンビン阻害剤よりも効率的でかつ、特異的な凝固系の阻害を期待できる。

従って、上記公知化合物とは化学構造が異なり、経口投与が可能であって、更に優れた効果を有する、選択的活性化血液凝固第Ｘ因子阻害剤の創製が切望されている。

発明の開示

本発明者等は、アミジノナフチルメチル基等が窒素原子を介してフェニル基若しくはピリジル基と結合した構造を有し、かつ、当該フェニル基若しくはピリジル基がヘキサヒドロ－１，４－ジアゼピン環の窒素原子に直接結合していることを化学構造上の特徴とする、下記一般式（Ｉ）で示されるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩が、優れた活性化血液凝固第Ｘ因子阻害作用を有することを見出し、本発明を完成した。

即ち、本発明は、下記一般式（Ｉ）で示されるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩、並びにそれらを有効成分とする医薬組成物、特に活性化血液凝固第Ｘ因子阻害剤に関する。



(I)

(但し、式中の記号は、下記の意味を有する。

A：フェニレン又はピリジレン基（これらは置換基を有してしてもよい）、

B：５乃至６員のアリール又はヘテロアリールを形成する、

X：－CO－、－CONH－、－CSNH－、－SO_2－、－SO_2NH－、又は式－SO_2N（－低級アルキル）－で示される基、

Y：結合又は低級アルキレン基

R^1：水素原子、低級アルキル、－L－アリール、－L－ヘテロアリール、－L－COO－R^6、－L－CON（－R^6）－R^7、－C（＝NH）－NH_2又は－C（＝NH）－低級アルキル基

R^2：水素原子、－O－低級アルキル、－COOH、－COO－低級アルキル、－$CONH_2$、－CONH－低級アルキル、－CON－ジ－低級アルキル基、或いは、アリール又はヘテロアリール基（これらは置換基を有していてよい）、

R^3：アミジノ基又は生体内でアミジノ基に転化されうる基

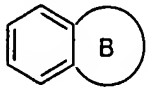
R^4，R^5：同一又は異なって、水素原子又は低級アルキル基

R^6，R^7：同一又は異なって、水素原子又は低級アルキル基

L：結合又は低級アルキレン基）

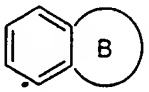
本発明化合物はヘキサヒドロ－１，４－ジアゼピニルフェニル（又はヘキサヒドロ－１，４－ジアゼピニルピリジル）が窒素原子を介してアミジノナフチルメチル基等と結合した構造を基本骨格とする点で、ピロリジニル（又はピペリジニル）オキシフェニル基が窒素原子を介してアミジノナフチルメチル基と結合した前記公知化合物とは明らかに構造が相違する。

本発明において好ましい化合物とは、上記一般式（Ｉ）において

環  が、ナフタレン又はベンゾフラン

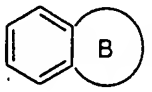
であるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩であり、又、R^4及びR^5が共に水素原子であるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩である。

更に好ましい化合物としては、一般式（Ｉ）において

環  が、ナフタレンであり、

Ａがフェニレン基（該フェニレン基はハロゲン原子、アミノ、シアノ、ニトロ、－ＯＨ、－ＣＯＯＨ、低級アルキル、－Ｏ－低級アルキル、又は－ＣＯＯ－低級アルキル基から選択される置換基を有していてもよい）又はピリジル基であり、R^3がアミジノ基であり、R^4及びR^5が共に水素原子であるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩である。

本発明化合物の内、特に好ましい化合物としては、一般式（Ｉ）において

環  が、ナフタレンであり、

Ａがフェニレン又はピリジレン基であり、Ｘが－ＣＯ－、－ＣＳＮＨ－、－SO_2－又は－SO_2NH－で示される基であり、R^1が水素原子、低級アルキル、ピリジル又は－Ｃ（＝ＮＨ）－CH_3基であり、R^2が水素原子、－ＣＯＯＨ、－ＣＯＯ－低級アルキル又はテトラゾリル基であり、R^3がアミジノ基であり、R^4及びR^5が共に水素原子であるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩である。

本発明化合物の内、最も好ましい化合物としては以下の化合物が挙げられる；Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕アセトアミド、

エチル　〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジ

アゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセテート、

エチル　Ｎ－〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕グリシネート、

エチル　Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕マロナメート、

〔Ｎ－〔６－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－ピリジル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセティックアシッド、

〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセティックアシッド、

Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スクシナミックアシッド、

エチル　Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－ピリジル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕マロナメート、

エチル　Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－ピリジル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スクシナメート、

Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕チオアミドアセティックアシッド、

Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－ピリジル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕

スクシナミックアシッド。

以下、本発明化合物（Ｉ）について詳細に説明する。

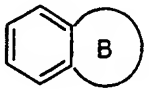
本明細書の一般式の基の定義において「低級」とは、特に断らない限り、炭素数１乃至６個を有する直鎖又は分枝状の炭素鎖を意味する。

従って、「低級アルキル基」とは炭素数が１乃至６個のアルキル基であり、具体的に例えばメチル，エチル，プロピル，ブチル，ペンテル，ヘキシル基又はイソプロピル基等のこれらの構造異性体であり、好ましくは炭素数１～４個のアルキル基であり、更に好ましくはメチル又はエチル基である。

「低級アルキレン基」とは、炭素数が１乃至６個の直鎖又は分岐状のアルキレン基であり、具体的にはメチレン，エチレン，トリメチレン，テトラメチレン，ペンタメチレン，ヘキサメチレン基又はこれらの構造異性体が挙げられ，好ましくは炭素数が１乃至３個のアルキレン基であり、更に好ましくはメチレン又はエチレン基である。

「アリール」とは炭素数６乃至１４個の芳香族環であって置換基を有していてもよく，具体的に例えば，ベンゼン，ナフタレン，アントラセン，フェナントレン基等が挙げられ，好ましくはベンゼン，ナフタレンである。

「ヘテロアリール」とはＮ，Ｏ又はＳ原子を１乃至４個有する５又は６員芳香族環或いは５又は６員芳香族環が縮合した二環であって置換基を有していてもよく，具体的に例えば，フラン，ピロール，チオフェン，イミダゾール，オキサゾール，チアゾール，ピリジン，ピリミジン，テトラゾール，ナフチリジン等が挙げられる。最も好ましいのは、Ｂとしてはフランであり、R^1としてはピリジル基であり、R^2としてはテトラゾリル基である。

環  としては、

具体的には、ナフタレン，ベンゾフラン，インドール，ベンゾチオフェン，ベンズイミダゾール，ベンズオキサゾール，ベンズチアゾール，キノリン，キナゾリンが挙げられ、好ましくはナフタレン又はベンゾフランである。

「アリール基」及び「ヘテロアリール基」の置換基、或いは「フェニレン又は

ピリジレン基」の置換基とは、アリール及びヘテロアリールの置換基として通常用いられる置換基であればいずれでもよく、例えば、低級アルキル（該低級アルキルはハロゲン原子、－Ｏ－低級アルキル、－ＣＯＯＨ、アミノ、－ＮＨ－低級アルキル及び－Ｎ－ジ－低級アルキル基からなる群より選択される１乃至４個の置換基で置換されていてもよい）、－ＯＨ、－Ｏ－低級アルキル、－ＣＯＯＨ、－ＣＯＯ－低級アルキル、ハロゲン原子、アミノ、シアノ、ニトロ、－ＮＨ－低級アルキル、－Ｎ－ジ－低級アルキル基が挙げられ、フェニレン基の置換基としては更に－Ｓ－低級アルキル、－ＳＯ－低級アルキル、－SO_2－低級アルキル、－$CONH_2$基及び－Ｏ－低級アルキレン－Ｏ－基等が挙げられ、１乃至３個の置換基を有していてもよい。好ましくは、ハロゲン原子、アミノ、シアノ、ニトロ、－ＯＨ、－ＣＯＯＨ、低級アルキル、－Ｏ－低級アルキル、又は－ＣＯＯ－低級アルキル基から選択される置換基が挙げられる。

「ハロゲン原子」としては，Ｆ，Ｃｌ，Ｂｒ又はＩ原子が挙げられる。

「生体内でアミジノ基に転化されうる基」とは、いわゆるプロドラッグ基を意味し、アミジノ基に－ＯＨ、－ＣＯＯ－低級アルキル基等が置換したもので、生理学的条件下において除去されてアミジノ基となるものを意味する。具体的には－Ｃ（－NH_2）＝Ｎ－ＯＨ、－Ｃ（－NH_2）＝Ｎ－ＣＯＯ－低級アルキル、並びに他のこの種の当業界で知られた基を包含する。

本発明化合物は置換基の種類によっては、二重結合に基づく、シス－トランス（又は（Ｅ）体、（Ｚ）体）の幾何異性体や互変異性体が存在する場合、また、不斉炭素原子が存在することによる（Ｒ）体、（Ｓ）体の光学異性体が存在する場合がある。本発明はこれらの幾何異性体、互変異性体、光学異性体の混合物や単離されたものを全て包含する。

本発明化合物（Ｉ）は、酸付加塩又は置換基の種類によっては塩基との塩を形成する場合もある。かかる塩としては、製薬学的に許容される塩であり、具体的には、塩酸、臭化水素酸、ヨウ化水素酸、硫酸、硝酸、リン酸等の無機酸、ギ酸、酢酸、プロピオン酸、シュウ酸、マロン酸、コハク酸、フマール酸、マイレン酸、乳酸、リンゴ酸、酒石酸、クエン酸、メタンスルホン酸、エタンスルホン酸、プロパンスルホン酸、トルエンスルホン酸、アスパラギン酸、グルタミン酸等の有機酸との酸付加塩、ナトリウム、カ

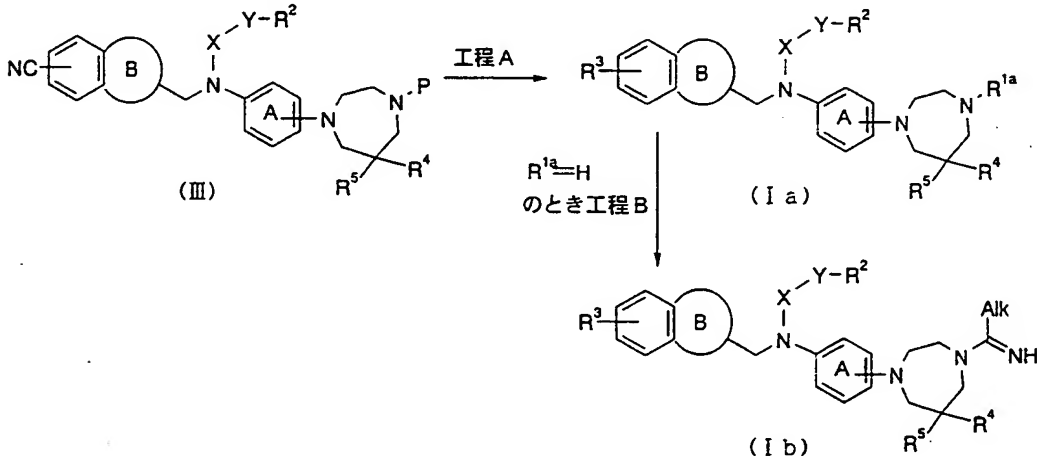
リウム、マグネシウム、カルシウム、アルミニウム等の無機塩基、メチルアミン、エチルアミン、エタノールアミン、リジン、オルニチン等の有機塩基との塩やアンモニウム塩等が挙げられる。これらの内で好ましいのは、塩酸塩、臭化水素酸塩、硫酸塩、リン酸塩、フマル酸塩、マレイン酸塩、クエン酸塩、メタンスルホン酸塩、エタンスルホン酸塩、プロパンスルホン酸塩又はトルエンスルホン酸塩である。

さらに、本発明は、本発明化合物（Ｉ）及びその塩の各種の水和物や溶媒和物及び結晶多形の物質をも包含する。

なお、当然のことながら、本発明は後記実施例に記載された化合物に限定されるものでなく、一般式（Ｉ）で示されるヘキサヒドロ－１，４－ジアゼピン誘導体又はその塩の全てを包含するものである。

（製造法）

以下、本発明化合物（Ｉ）の代表的な製造法を説明する。



（式中、Ａ、Ｂ、R^2、R^3、R^4、Ｘ及びＹは前記の意味を有し、 Alk は低級アルキル基を、R^{1a}は水素原子又はピリジル基を、Ｐはピリジル基又はアミノ基の保護基を意味する。）

Ｐに例示されるアミノ基の保護基としては、通常、アミノ基の保護に用いられる基であれば特に制限はなく、例えば、－ＣＯＯ－低級アルキル、－ＣＯＯ－低級アルキル－アリール、アシル、低級アルキル、－低級アルキル－アリール、－SO_2－低級アルキル基等が挙げられる。

〔工程Ａ〕

本発明化合物中、R^1が水素原子又はピリジル基である化合物（Ｉａ）は、以下①～③に掲げる方法により合成することができる。

①ニトリルをイミデートに変換した後、アミンと縮合させる方法：

ニトリル体（Ⅲ）に塩酸ガス存在下、メタノールやエタノール等のアルコールを－４０℃乃至０℃で作用させ、イミデートに変換した後、アンモニア、炭酸アンモニウム、塩化アンモニウム、酢酸アンモニウム等のアミン又はアミン塩を反応させる。溶媒は反応に有利な溶媒、若しくは不活性溶媒が用いられる。不活性溶媒としては、テトラヒドロフラン（ＴＨＦ）、Ｎ，Ｎ－ジメチルホルムアミド（ＤＭＦ）、ジメチルスルホキシド（ＤＭＳＯ）、ベンゼン、トルエン、キシレン、酢酸エチル、アセトン、アセトニトリル、ジクロロメタン、ジクロロエタン、クロロホルム、メタノール、エタノール、イソプロパノール又はこれらの混合溶媒等が挙げられる。

②ニトリルを、チオアミドを経由してチオイミデートに変換し、アミンと縮合させる方法：

ニトリル体（Ⅲ）にメチルアミン、トリエチルアミン、ピリジン、ピコリン等の有機塩基の存在下で硫化水素を作用させ、又はニトリル体（Ⅲ）に塩化水素の存在下でジチオリン酸ｏ，ｏ－ジエチルを作用させ、チオアミド体に誘導する。次いで、前記チオアミド体にヨウ化メチル、ヨウ化エチル等の低級アルキルハロゲン化物を反応させ、チオイミデート体に変換し、アンモニア、炭酸アンモニウム、塩化アンモニウム、酢酸アンモニウム等のアミン又はアミン塩を反応させる。溶媒としては、前記の不活性溶媒が用いられる。

③ニトリルにアミン、アミン塩、金属アミド、グルニャール試薬を直接付加させる方法：

ニトリル体（Ⅲ）にアンモニア、塩化アンモニウムとアンモニア、チオシアン酸アンモニウム、チオシアン酸アルキルアンモニウム、ＭｅＡｌ（Ｃｌ）NH_2、$NaNH_2$、$(CH_3)_2NMgBr$等の試薬を付加させる。前記反応は、前記の不活性溶媒中で又は無溶媒で行うことができる。また、水素化ナトリウム等の塩基又は塩化アルミニウム、ｐ－トルエンスルホン酸等の酸を触媒として添加する

ことにより、反応が著しく加速される場合がある。なお、反応は冷却乃至室温乃至加温下で行うことができる。

ニトリルをアミジノ基に変換する反応中において、Pに例示されるアミノ基の保護基が切断されない場合がある。その場合には、更にその保護基を切断するのに適した方法で切断することにより本発明化合物（Ｉａ）を得ることができる。

また、化合物（Ⅲ）に－ＣＯＯ－アルキル基が結合している場合には、このアミジノ化反応と同時に－ＣＯＯ－アルキル基を－ＣＯＮＨ$_3$基に変換することも可能である。

〔工程Ｂ〕

本発明化合物中、Ｒ^{1}が－Ｃ（＝ＮＨ）－低級アルキル基である化合物（Ｉｂ）は、塩基存在下において、前記第１工程で製造される、本発明化合物中（Ｉａ）中、２級アミノ基を有する化合物（Ｒ^{1a}＝Ｈ）に対し、イミデート化合物を反応させることにより、合成することができる。

前記反応は、冷却下乃至加熱下で行うことができ、前記の不活性溶媒を用いることができる。また、塩基としては、Ｎ－メチルモルホリン、トリエチルアミン、トリメチルアミン、ピリジン、ピコリン、ルチジン、ジメチルアニリン等の有機塩基、水酸化ナトリウム、水酸化カリウム、炭酸水素ナトリウム等の無機塩基を用いることができる。

なお、化合物（Ｉｂ）に－ＣＯＯ－アルキル基が結合している場合には、必要に応じ、塩基性条件下、酸性条件下あるいは中性条件下の加水分解反応により、カルボキシル基に変換することができる。

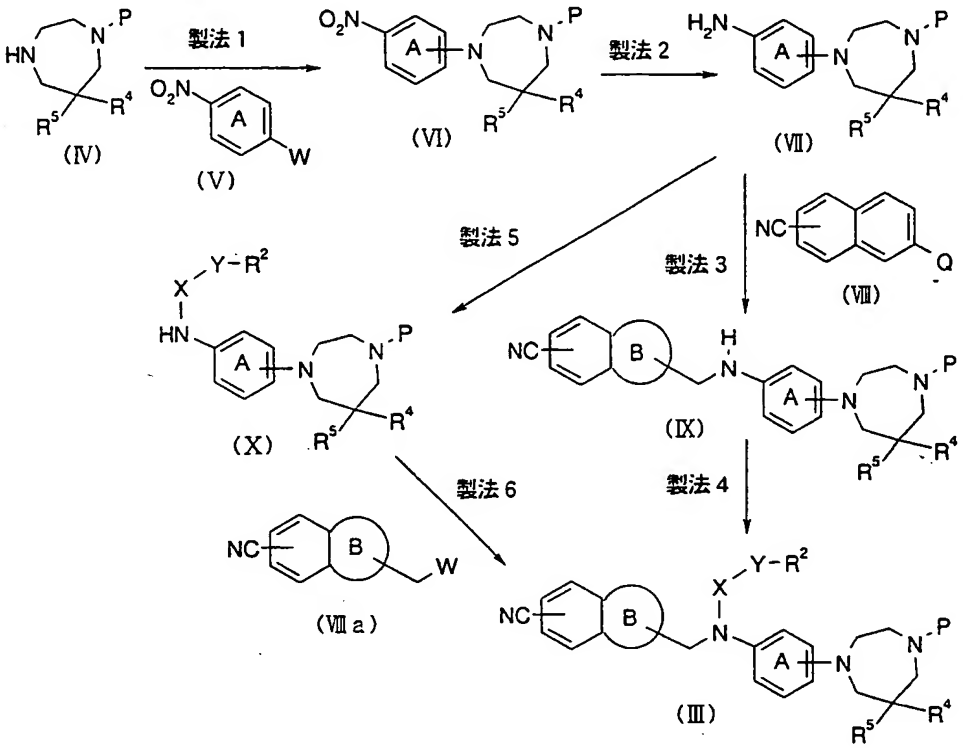
前記加水分解反応においては、塩基性条件下では、水酸化ナトリウム、水酸化カリウム、水酸化リチウム、水酸化バリウム等の塩基、酸性条件下では、塩酸、硫酸、三塩化ホウ素などのルイス酸、ｐ－トルエンスルホン酸等の酸、中性条件下ではヨウ化リチウム、臭化リチウムなどのハロゲンイオン、チオールおよびセレノールのアルカリ金属塩、ヨードトリメチルシラン、およびエステラーゼのような酵素等を用いることができる。

前記の不活性溶媒を用い、反応は通常室温にて進行するが、氷冷下、あるいは

加熱下における反応を要するものもある。これらは、常法により適宜選択して行うことができる。

（原料化合物の製造法）

以下、本発明化合物（Ｉ）の原料化合物について代表的な製造法を説明する。



（式中、Ａ、Ｂ、R^2、R^4、R^5、Ｘ、Ｙ及びＰは前記の意味を有し、Ｗはハロゲン原子又は有機スルホン酸残基を、Ｑはアルデヒド基又は式－CH_2－Ｗで示される基を、Ｐ’はＰ又は水素原子を意味する。）

製法１

本反応はヘキサヒドロ－１，４－ジアゼピン誘導体（Ⅳ）とニトロベンゼン又はニトロピリジン誘導体（Ⅴ）とを反応させ、化合物（Ⅵ）を合成する反応である。本反応は、通常の置換反応と同様であり、無溶媒又は前記の不活性な有機溶媒中、室温乃至加熱下、あるいは加熱還流下に行われ、必要に応じて前記の無機塩基の存在下で行う。Ｐ’が水素原子の場合はクロロピリジン等を用い、同様な置換反応を更に行うことにより、Ｐがピリジル基である化合物（Ⅵ）を合成できる。　また、アミノ基の保護基をそれに適した方法で更に導入することにより、

Pがアミノ基の保護基である化合物（VI）を合成することができる。

製法２

本反応はニトロ体（VI）からアミン体（VII）を得る反応である。本反応は、常法による還元法により行うことができるが、具体的には、亜鉛やスズ等の金属を用いる方法、$LiAlH_4$等の金属水素化物を用いる方法、パラジウム－炭素等を用いる接触還元法等を用いることができる。これらの反応は、前記の不活性溶媒中で、室温乃至加温下で行われる。

製法３

本反応は常法のＮ－アルキル化反応法に従えばよい。

（ｉ）化合物（VIII）がアルキルハライド又はアルキルスルホネートの場合：本反応は化合物（VII）と反応対応量の化合物（VIII）とを前記の不活性溶媒中、冷却下乃至加熱下撹拌しながら行われる。反応を促進させるには前記の塩基を添加するのが好ましい。

（ｉｉ）化合物（VIII）がアルデヒドの場合：本反応は、還元的アミノ化反応であり、化合物（VII）と対応するアルデヒド（VIII）と還元剤とを反応させる。この還元剤としては、例えば水素化ホウ素ナトリウム、水素化シアノホウ素ナトリウム、トリアセトキシ水素化ホウ素ナトリウム等が用いられる。本反応は、アルコール又は前記の不活性溶媒中、冷却下乃至加熱下（還流下）撹拌しながら行われる。

製法４

原料化合物（III）は、以下（ａ）～（ｃ）で示される方法により製造できる。

（ａ）アミド化合物（IIIａ）の製造法

原料化合物（III）中、Ｘが－ＣＯ－で示されるアミド化合物（IIIａ）は、アミン（IX）とカルボン酸の活性誘導体（例えば酸クロライド等）とのアシル化反応により合成することができる。

また、アミド化合物（IIIａ）は、縮合剤の存在下、アミン（IX）とカルボン酸とのアシル化反応によっても合成することができる。縮合剤としては、Ｎ，Ｎ－ジシクロヘキシルカルボジイミド（ＤＣＣ）、１－エチル－３－（３－（Ｎ，Ｎ－ジメチルアミノ）プロピル）カルボジイミド、カルボニルジイミダゾール等を

好適に用いることができる。通常、前記反応は、前記の不活性溶媒中において冷却下乃至室温下に行ない、アシル化反応の種類によっては無水の条件下に行う。また、前記の塩基の存在下で又はこれら塩基を溶媒として反応することにより、反応が円滑に進行する場合がある。

（ｂ）ウレア化合物（Ⅲｂ）の製造法

原料化合物（Ⅲ）中、Ｘが－ＣＯＮＨ－であるウレア化合物（Ⅲｂ）は、アミン（Ⅸ）とイソシアネート誘導体とを反応させることにより、又、アミン（Ⅸ）とホスゲン、ジホスゲン又はトリホスゲン等との反応によりカルバモイルクロライドを得た後、アミン誘導体と反応させることにより、合成することができる。

前記反応は、前記の不活性溶媒中において、冷却下乃至還流下で行うことができ、適用する方法に応じ適宜選択するのが好ましい。

また、前記の塩基の存在下で又はこれら塩基を溶媒として反応することにより、反応が円滑に進行する場合がある。

（ｃ）スルホンアミド化合物又はスルファミド化合物（Ⅲｃ）の製造法

原料化合物（Ⅲ）中、X^1が－SO_2－又は－SO_2NH－で示されるスルホンアミド化合物又はスルファミド化合物（Ⅲｃ）は、アミン（Ⅸ）とスルホニルハライド誘導体及びスルホン酸無水物を通常は前記の塩基の存在下で反応することにより合成することができる。前記反応は、前記の不活性溶媒中で冷却下乃至還流下において行うことができ、適用する方法に応じ適宜選択するのが好ましい。

製法５

化合物（Ⅶ）のＸが－ＣＯ－、－ＣＯＮＨ－、－SO_2－又は－SO_2NH－で示される基である場合には、前記製法４（ａ）～（ｃ）と同様の方法で化合物（Ｘ）を合成することができる。反応温度、溶媒等の反応条件においても前記製法４（ａ）～（ｃ）と同様である。

製法６

本製法中、化合物（Ⅷａ）と化合物（Ｘ）とを反応させて化合物（Ⅲ）を合成する反応は前記製法３（ｉ）と同様である。反応温度、溶媒等の反応条件においても前記製法３（ｉ）と同様である。

また、本発明の原料化合物は、その他公知のアルキル化、酸化、還元、加水分解等当業者が通常採用し得る工程を任意に組み合わせることにより製造することができる。例えばアルキル化法によれば、スルホンアミド化合物とその反応量乃至過剰量のアルコール（メタノール又はエタノール等）を、トリフェニルホスフィン及びジエチルアゾカルボキシレートの存在下、前記の不活性溶媒中において、室温乃至加温下で撹拌しながら反応することにより、アルキル置換スルホンアミド体を得ることができる。

このようにして製造された本発明化合物は、周知の方法、例えば、抽出、沈殿、分画クロマトグラフィー、分別結晶化、再結晶等により単離、精製することができ、通常の造塩反応に付すことにより所望の塩に導くことができる。

また、本発明化合物が不斉炭素原子を有する場合には光学異性体が存在するが、これらの光学異性体は、適切な塩と再結晶する分別結晶化やカラムクロマトグラフィ等の常法により分割することができる。

産業上の利用可能性

本発明化合物は、活性化血液凝固第Ｘ因子を特異的に阻害し、強力な抗凝固作用を有する。従って、血液凝固抑制剤又は血栓若しくは塞栓によって引き起こされる疾病の予防・治療剤として有用である。適応する上記疾病としては、脳梗塞、脳血栓、脳塞栓(N Engl J Med, 333, 1588-1593, 1995)、急性及び慢性心筋梗塞、不安定狭心症(Thromb Haemost, 74, 640-645, 1995)、冠動脈血栓溶解等の虚血性心疾患における疾病(Cardiovasc Res, 28, 78-85, 1994 / J Am Coll Cardiol, 28, 1858-1865, 1996)、末梢動脈閉塞症(Fibrinolysis, 7, 195-202, 1993)、深部静脈血栓症(Thromb Haemost, 65, 257-262, 1991 / Thromb Res, 71, 317-324, 1993)、汎発性血管内凝固症候群(Thromb Haemost, 72, 393-396, 1994)、人工血管術後及び人工弁置換後の血栓形成症、冠動脈バイパス術後における再閉塞及び再狭窄症(Circulation, 84, 1741-1748,1991)、PTCA後再狭窄(Circulation, 89, 1262-1271, 1994 / Circulation, 93, 1542-1548, 1996)、体外循環時の血栓形成症(Thromb Haemost, 74, 635-639, 1995)等の各種血管障害における疾病等が挙げられる。また、本発明化合物の活性化血液凝固第Ｘ因子阻害作用により、インフルエンザウ

イルスの増殖阻害活性に基づくインフルエンザウイルスの感染予防・治療剤としての可能性が示唆される(特開平 6-227971 号)。

なお、本発明の化合物の優れた活性化血液凝固第Ｘ因子阻害活性については、以下に示す試験方法により確認された。

１）ヒト活性化血液凝固第Ｘ因子凝固時間測定法

ヒト活性化血液凝固第Ｘ因子（コスモバイオ社）を０．０５Ｍトリス塩酸緩衝液（pH=7.40）に溶解し、0.05 単位/ml を作成する。３．８％クエン酸ナトリウム１／１０容にて採血し、3000rpm で 10 分の遠心処理により分離したヒト血漿 90 μｌおよび生理食塩水にて溶解希釈した薬剤 10 μｌ、上記活性化血液凝固第Ｘ因子溶液 50 μｌを添加 37℃にて３分間加温し、20mM $CaCl_2$ 溶液 100 μｌを添加し凝固時間の測定を行なった。

凝固時間の測定にはＡｍｅｌｕｎｇ社ＫＣ４Ａを使用した。凝固時間２倍延長用量（ＣＴ２と略す）は、薬剤の代わりに生理食塩水 10 μｌを添加した場合の凝固時間をもとに算出した。この結果を表１に示す。

表１

実施例番号	ヒト活性化血液凝固第Ｘ因子凝固時間測定試験 ＣＴ２(μＭ)
１７	０．０９２
２２	０．１１１
２３	０．１１０
２４	０．１５２
３２	０．０８９
３３	０．０９８
３６	０．０６９
７２	０．１１９
７３	０．２２４
７５	０．０９５
８４	０．１３４
対照化合物	０．５９０

＊）対照化合物：特開平５－２０８９４６号の実施例５２の化合物

本発明の化合物は、ヒト活性化血液凝固第Ｘ因子を特異的に阻害し、低濃度で凝固時間を延長し、優れた抗血液凝固作用を示すことが確認された。

2）マウスを用いたｅｘｏ　ｖｉｖｏでの凝固時間測定法（静脈内投与）

12時間以上絶食した雄性ＩＣＲマウス（20−30ｇ、ＳＬＣ社）に対し、生理食塩水にて溶解した薬剤を尾静脈より単回投与し、1分後にジエチルエーテル麻酔下で、後大動脈より3.8％クエン酸ナトリウム１／１０容にて0.6ml採血し、3000rpmで10分の遠心処理により血漿を分離した。この血漿を用いて以下ａ）及びｂ）の方法に従い、外因系凝固時間（ＰＴ）および内因系凝固時間（ＡＰＴＴ）の測定を行った。

ａ）外因系凝固時間（ＰＴ）

組織トロンボプラスチン（54mg/vial、凍結乾燥製剤、オルソ社）を蒸留水2.5mlに溶解し37℃にて予備加温した。上記血漿50μｌを37℃にて1分間加温し、上記トロンボプラスチン溶液50μｌを添加し凝固時間の測定を行った。凝固時間の測定にはＡｍｅｌｕｎｇ社ＫＣ４Ａを使用した。薬剤の代わりに生理食塩水50μｌを添加した場合の凝固時間をコントロールとし、このコントロールを１としたときの相対値で薬剤の活性を示した。

ｂ）内因系凝固時間（ＡＰＴＴ）

活性トロンボファックス（オルソ社）50μｌ、上記血漿50μｌを37℃にて3分間加温し、あらかじめ37℃にて予備加温した20mM　$CaCl_2$溶液50μｌを添加し凝固時間の測定を行った。凝固時間の測定にはＡｍｅｌｕｎｇ社ＫＣ４Ａを使用した。薬剤の代わりに生理食塩水を投与した場合の凝固時間をコントロールとし、このコントロールを１とした時の相対値で薬剤の活性を示した。なお、抗凝固作用の用量依存性および経時変化に関しても、投与用量あるいは採血時間を変更し同様の方法にて検討した。

本試験の結果、本発明化合物は静脈内投与において良好な凝固時間の延長作用が認められた。

3）マウスを用いたｅｘｏ　ｖｉｖｏでの凝固時間測定法（経口投与）

上記２）の試験で尾静脈の単回投与の代わりに経口ゾンデを用いて強制経口投与し30分後に採血した他は、上記２）の試験と同様に行った。

本試験の結果、本発明化合物は、経口投与においても凝固時間の延長作用が認

められた。

4）カニクイザルを用いたｅｘｏ　ｖｉｖｏでの凝固時間測定法（経口投与）

12時間以上絶食した雄性カニクイザル（3－6ｋｇ、ハムリー）に対し、生理食塩水にて溶解、又は0.5％メテルセルロース溶液にて懸濁した薬剤をgastric tubeを用いて強制経口投与し、経時的に無麻酔下で大腿静脈より3.8％クエン酸ナトリウム１／１０容にて3ml採血し、3000rpmで10分の遠心処理により血漿を分離した。この血漿を用いて上記2）と同様に、外因系凝固時間（ＰＴ）および内因系凝固時間（ＡＰＴＴ）の測定を行った。

本試験の結果、本発明化合物は、経口投与においても良好なバイオアベイラビリティを示し、優れた凝固時間の延長作用が認められた。

一般式（Ｉ）で示される本発明化合物やその製薬学的に許容される塩の１種又は２種以上を有効成分として含有する医薬組成物は、通常用いられている製剤用の担体や賦形剤、その他の添加剤を用いて、錠剤、散剤、細粒剤、顆粒剤、カプセル剤、丸剤、液剤、注射剤、坐剤、軟膏、貼付剤等に調製され、経口的又は非経口的に投与される。

本発明化合物のヒトに対する臨床投与量は適用される患者の症伏、体重、年令や性別等を考慮して適宜決定されるが、通常成人１日当り経口で0.1～500mg、非経口で0.01～100mgであり、これを１回あるいは数回に分けて投与する。投与量は種々の条件で変動するので、上記投与量範囲より少ない量で十分な場合もある。

本発明による経口投与のための固体組成物としては、錠剤、散剤、顆粒剤等が用いられる。このような固体組成物においては、一つ又はそれ以上の活性物質が少なくとも一つの不活性な希釈剤、例えば乳糖、マンニトール、ブドウ糖、ヒドロキシプロピルセルロース、微結晶セルロース、デンプン、ポリビニルピロリドン、メタケイ酸、アルミン酸マグネシウムと混合される。組成物は、常法に従って、不活性な希釈剤以外の添加剤、例えばステアリン酸マグネシウムのような潤滑剤や繊維素グリコール酸カルシウムのような崩壊剤、ラクトースのような安定化剤、グルタミン酸又はアスパラギン酸のような可溶化乃至は溶解補助剤を含有していてもよい。錠剤又は丸剤は必要によりショ糖、ゼラチン、ヒドロキシプロ

ピルセルロース、ヒドロキシプロピルメチルセルロースフタレートなどの胃溶性あるいは腸溶性物質のフィルムで被膜してもよい。

経口投与のための液体組成物は、薬剤的に許容される乳濁剤、溶液剤、懸濁剤、シロップ剤、エリキシル剤等を含み、一般的に用いられる不活性な希釈剤、例えば精製水、エチルアルコールを含む。この組成物は不活性な希釈剤以外に可溶化乃至溶解補助剤、湿潤剤・懸濁剤のような補助剤、甘味剤、風味剤、芳香剤、防腐剤を含有していてもよい。

非経口投与のための注射剤としては、無菌の水性又は非水性の溶液剤、懸濁剤、乳濁剤を包含する。水性の溶液剤、懸濁剤の希釈剤としては、例えば注射剤用蒸留水及び生理食塩水が含まれる。非水溶性の溶液剤、懸濁剤の希釈剤としては、例えばプロピレングリコール、ポリエチレングリコール、オリーブ油のような植物油、エチルアルコールのようなアルコール類、ポリソルベート８０（商品名）等がある。このような組成物は、さらに等張化剤、防腐剤、湿潤剤、乳化剤、分散剤、安定化剤（例えば、ラクトース）、可溶化乃至溶解補助剤のような添加剤を含んでもよい。これらは例えばバクテリア保留フィルターを通す濾過、殺菌剤の配合又は照射によって無菌化される。これらは又無菌の固体組成物を製造し、使用前に無菌水又は無菌の注射用溶媒に溶解して使用することもできる。

本発明化合物の溶解性が低い場合には、可溶化処理を施してもよい。可溶化処理としては、医薬製剤に適用できる公知の方法、例えば界面活性剤（ポリオキシエチレン硬化ヒマシ油類等）を添加する方法、薬物と可溶化剤（例えばヒドロキシプロピルメチルセルロース等の水溶性高分子、カルボキシメチルエチルセルロース等の腸溶性高分子）との固体分散体を形成する方法が挙げられる。更に必要により、可溶性の塩にする方法、サイクロデキストリン等を用いて包接化合物を形成させる方法等も採用できる。可溶化の手段は、目的とする薬物に応じて適宜変更できる（「最近の製剤技術とその応用」，医薬ジャーナル，157-159(1983)及び「薬学モノグラフ No.1，生物学的利用能」，ソフトサイエンス社，78-82(1988)）。このうち、好ましくは、薬物と可溶化剤との固体分散体を形成させ溶解性を改善する方法が採用される（特開昭 56－49314 号，ＦＲ 2460667 号）。

発明を実施するための最良の方法

以下、本発明化合物の製造例を掲げ、本発明化合物の製造方法を具体的に説明する。本発明化合物は、下記実施例に記載の化合物に限定されるものではなく、また、前記一般式（Ｉ）に示される化合物、その塩、その水和物、その溶媒和物、その互変並びに光学異性体、結晶多形の全てを包含するものである。尚、本発明化合物の原料化合物には新規な化合物も含まれており、これらの化合物の製造方法を参考例として説明する。

参考例１

１－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン1.8gをＤＭＦ 10mlに溶解し、これに４－フルオロニトロベンゼン1.62g及び炭酸カリウム1.84gを加え、90℃で13時間撹拌した。反応液を冷却後、酢酸エチルを加え、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣を１，４－ジオキサン 10mlに溶解し、これに４Ｎ塩酸（１，４－ジオキサン溶液）4mlを加え、80℃で16時間撹拌した。反応液を冷却後、留去し、得られた残渣にジエチルエーテル50mlを加えた後濾過し、１－（４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン・２塩酸塩2.11gを得た。

参考例２

参考例１の化合物2gをイソアミルアルコール20mlに溶解し、これに４－クロロピリジン・塩酸塩1.02g及び炭酸水素ナトリウム2.57gを加え24時間過熱還流を行った。更に反応液に４－クロロピリジン・塩酸塩500mgを加え24時間過熱還流を行った。反応液を冷却後、留去し、得られた残渣にクロロホルムを加え水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣を１，４－ジオキサン30mlに溶解し、これにトリエチルアミン0.95ml及びジ－ｔ－ブチルジカルボネート1.48gを加え、室温にて12時間撹拌した。反応液を留去し、得られた残渣をクロロホルム：メタノール（１０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、１－（４－ニトロフェニル）－４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン1.94mgを得た。

参考例３

10%パラジウムーカーボン粉末 100mg をメタノール 1ml に懸濁し、これに参考例 2 の化合物 460mg をメタノール 20ml に溶解した溶液を加え、水素雰囲気下、室温で 8 時間撹拌した。反応液をセライト濾過し、濾液を留去した。得られた残渣を１，２－ジクロロエタン 20ml に溶解し、これに、７－ホルミル－２－ナフタレンカルボニトリル 290mg、酢酸 0.41ml 及びソディウムトリアセトキシボロヒドリド 458mg を加え、室温で 21 時間撹拌した。反応液にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（１０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、７－〔〔４－〔４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕アニリノ〕メチル〕－２－ナフタレンカルボニトリル 429mg を得た。

参考例 4

参考例 3 の化合物 420mg を１，２－ジクロロエタン 10ml に溶解し、これにトリエチルアミン 0.2ml 及びメタンスルホニルクロライド 0.11ml を加え室温で 12 時間撹拌した。反応液にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（２０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、Ｎ－〔（７－シアノ－２－ナフチル）メチル〕－Ｎ－〔４－〔４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕フェニル〕メタンスルホンアミド 340mg を得た。

参考例４と同様にして、表１０の参考例５～６の化合物を得た。

参考例 7

４－フルオロ－３－メチルニトロベンゼン 3.0g をＤＭＦ 20ml に溶解し、これにヘキサヒドロ－１Ｈ－１，４－ジアゼピン 5.81g 及び炭酸カリウム 3.94g を加え、90℃で 4 時間撹拌した。

反応液を冷却後、クロロホルムを加え、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（５：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、１－（２

－メチル－４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 3.78g を得た。

参考例７と同様にして、表７の参考例８～１０の化合物を得た。

参考例１１

参考例１０で得た５－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－２－ニトロベンゾニトリル 5.8g をエタノール 20ml に溶解し、これに 6 M水酸化ナトリウム水溶液を加えて、15 時間加熱還流した。反応液を冷却し、濃塩酸で中和後、留去した。得られた残渣をメタノール 150ml に溶解し、これに硫酸 10ml を加え、２日間加熱還流した。反応液を冷却後、留去し、得られた残渣を少量の水に溶解し、炭酸ナトリウムで中和した。これにクロロホルムを加え飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後、留去し、メチル　５－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－２－ニトロベンゾエート 4.21g を得た。

参考例１２

ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 21.4g をＤＭＦ 214ml に溶解し、これに４－フルオロニトロベンゼン 10.1g 及び炭酸カリウム 19.7g を加え、90℃で７時間撹拌した。反応液を留去し、得られた残渣にクロロホルムを加え、10%炭酸水素カリウム水溶液、飽和食塩水で順次洗い、無水硫酸マグネシウムで乾燥した後、溶媒を留去した。得られた残渣を１，２－ジクロロエタン 210ml に溶解し、これにトリエチルアミン 86.5g、ジ－ｔ－ブチルジカルボネート 93.4g を加え、室温で 13 時間撹拌した。反応液を水で洗い、無水硫酸ナトリウムで乾燥後、留去した。残渣をエーテルで洗い、４－ｔ－ブトキシカルボニル－１－（４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 14.12g を得た。

参考例１２と同様にして、表８の参考例１３～１４の化合物を得た。

参考例１５

参考例７の化合物 3.7g を１，４－ジオキサン 50ml に溶解し、これにトリエチルアミン 3.23ml、ジ－ｔ－ブチルジカルボネート 5.2g を加え、室温で 90 分撹拌した。反応液を留去し、得られた残渣にクロロホルムを加え、水、飽和食塩水で

順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（５０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにより精製し、４－ｔ－ブトキシカルボニル－１－（２－メチル－４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 7.64g を得た。

参考例１５と同様にして、表８の参考例１６～１８の化合物を得た。

参考例１９

参考例１２で得た４－ｔ－ブトキシカルボニル－１－（４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 14.12g をエタノール 44ml に懸濁し、10%パラジウム－炭素 700mg を加え水素雰囲気下室温で 16 時間撹拌した。反応液を濾過した後、留去し、得られた残渣を１，２－ジクロロエタン 440ml に溶解した後に、７－ホルミル－２－ナフタレンカルボニトリル 7.95g と酢酸 26ml、ソジウムトリアセトキシボロヒドリド 18.5g を順次加え、室温で 2 時間撹拌した。

７－ホルミル－２－ナフタレンカルボニトリル 0.8g とソジウムトリアセトキシボロヒドリド 1.9g を加え、更に 1 時間撹拌した。更に７－ホルミル－２－ナフタレンカルボニトリル 0.8g とソジウムトリアセトキシボロヒドリド 1.9g を加え、2 時間撹拌した。反応液を 10%炭酸カリウム水溶液、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥した後、留去した。得られた残渣 25.01g のうち、7.04g をヘキサン：酢酸エチル（３：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、７－〔〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）アニリノ〕メチル〕－２－ナフタレンカルボニトリル 4.45g を得た。

参考例２０

参考例１５の化合物 2.1g をメタノール 10ml に溶解し、10%パラジウム－炭素 300mg 及び蟻酸アンモニウム 2.1g を加え室温で 5 時間撹拌した。

反応液をセライト濾過した後濾液を留去した。得られた残渣にクロロホルムを加え、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣を１，２－ジクロロエタン 20ml に溶解し、７－ホルミル－２－ナフタレンカルボニトリル 835mg と酢酸 1.28ml 及びソジウムトリアセトキシボロヒ

ドリド 1.5g を順次加え、室温で 14 時間撹拌した。反応液にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（３０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、７－〔〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－メチルアニリノ〕メチル〕－２－ナフタレンカルボニトリル 1.94g を得た。

参考例２１－１

参考例１６で得た１－ｔ－ブトキシカルボニル－４－（２－クロロ－４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 2.1g を４Ｎ塩酸－１，４－ジオキサン溶液 10ml に溶解し、80℃で 2 時間撹拌した。反応液を留去し、得られた残渣にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。

得られた残渣を１，２－ジクロロエタン 20ml に溶解し、これにベンズアルデヒド 0.6ml、酢酸 1.65ml 及びソディウムトリアセトキシボロヒドリド 1.9g を加え、室温で１７時間撹拌した。反応液にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。

得られた残渣をクロロホルム：メタノール（４０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、４－ベンジル－１－（２－クロロ－４－ニトロフェニル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 1.47g を得た。

参考例２１－２

参考例２１－１の化合物 1.4g をエタノール 20ml 及び水 20ml に溶解し、これに還元鉄 2.26g 及び塩化アンモニウム 108mg を加え、3 時間加熱還流した。反応液を冷却後、セライト濾過し、留去した。

得られた残渣にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣を１，２－ジクロロエタン 20ml に溶解し、これに７－ホルミル－２－ナフタレンカルボニトリル 684mg、酢酸 1.05ml、ソディウムトリアセトキシボロヒドリド

1.24g を加え、室温で 24 時間撹拌した。

反応液にクロロホルムを加え、飽和炭酸水素ナトリウム水溶液、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（５０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、７－〔〔４－（４－ベンジルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－クロロアニリノ〕メチル〕－２－ナフタレンカルボニトリル 1.61g を得た。

参考例２１－３

参考例２１－２の化合物 642mg を１，２－ジクロロエタン 20ml に溶解し、これに１－クロロエチルクロロホルメート 1.44ml を加え、90℃で 16 時間撹拌した。反応液を冷却後留去し、得られた残渣をメタノール 20ml に溶解し、2 時間加熱還流した。反応液を冷却後留去し、得られた残渣を１，４－ジオキサン 20ml に溶解し、これにジ－ｔ－ブチルジカルボネート 270mg 及びトリエチルアミン 0.21ml を加え、室温で 7 時間撹拌した。

反応液を留去し、得られた残渣をヘキサン：酢酸エチル（４：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、７－〔〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－クロロアニリノ〕メチル〕－２－ナフタレンカルボニトリル 298mg を得た。 参考例１９と同様にして、表９の参考例２２～２３の化合物を得た。

参考例２４

参考例１９で得た７－〔〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）アニリノ〕メチル〕－２－ナフタレンカルボニトリル 400mg を１，２－ジクロロエタン 5ml に溶解し、3℃で撹拌した。これにピリジン 208mg 及びメタンスルホニルクロライド 201mg を加えた後、室温で 12 時間撹拌した。反応液にクロロホルムを加え飽和炭酸水素ナトリウム水溶液、水、10%クエン酸水溶液、水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をメタノールより再結晶し、Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ

－〔（７－シアノ－２－ナフチル）メチル〕メタンスルホンアミド 342mg を得た。

参考例２４と同様にして、表１０の参考例２５～３５及び参考例４０の化合物を得た。

参考例３６

参考例１９の化合物 509mg を１，２－ジクロロエタン 5ml に溶解し、エトキシカルボニルイソシアネート 401mg を加え室温で 3 時間撹拌した。反応液に 10%クエン酸水溶液を加えクロロホルムで抽出し、有機層を無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をエタノール：クロロホルム（２：９８）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにて精製し、エチル　Ｎ－〔Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕カルバモイル〕カルバメート 637mg を得た。

参考例３７

参考例１３で得た４－ｔ－ブトキシカルボニル－１－（２－フルオロ－４－ニトロフェニル)ヘキサヒドロ－１Ｈ－１，４－ジアゼピン 1.62g をエタノール 48ml に懸濁し、10%パラジウム－炭素 160mg を加え水素雰囲気下室温で 2 時間撹拌した。反応液を濾過した後、留去した。得られた残渣の 1.62g のうち 0.61g を１，２－ジクロロエタン 20ml に溶解し、７－ホルミル－２－ナフタレンカルボニトリル 357mg と酢酸 1.2g、ソジウムトリアセトキシボロヒドリド 823mg を順次加え、室温で 2 時間撹拌した。反応液を 10%炭酸カリウム水溶液、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥した後、留去した。得られた残渣を１，２－ジクロロエタン 20ml に溶解し、ピリジン 467mg、エチル　クロロスルホニルアセテート 560mg を 0℃で加え 1 時間撹拌した。エタノール 1ml を加え 1 時間撹拌した後反応液を濃縮した。得られた残渣をヘキサン：酢酸エチル（３：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、エチル　〔Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－フルオロフェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕スルファモイル〕アセテート 1.08g を得た。

参考例３７と同様にして、表１０の参考例３８の化合物を得た。

参考例３９

参考例２７で得たｔ－ブチル　Ｎ－〔Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕スルファモイル〕カルバメート 1.7g をＤＭＦ 20ml に溶解し、これにブロモ酢酸エチル 0.44ml 及び炭酸カリウム 543mg を加え、室温で 24 時間撹拌した。反応液にクロロホルムを加え、水、飽和食塩水で順次洗い、無水硫酸ナトリウムで乾燥後、留去した。得られた残渣をクロロホルム：メタノール（３０：１）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製し、エチル　Ｎ－〔Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕スルファモイル〕－Ｎ－ｔ－ブトキシカルボニルグリシネート 1.68g を得た。

実施例１

参考例４で得たＮ－〔（７－シアノ－２－ナフチル）メチル〕－Ｎ－〔４－〔４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕フェニル〕メタンスルホンアミド 330mg をクロロホルム 2ml 及びエタノール 10ml の混合液に溶解した。この溶液を撹拌下－20℃に冷却し、塩化水素を導入し飽和させた。この反応液を 5℃で 17 時間撹拌した後、反応液を留去した。得られた残渣をエタノール溶液 10ml に溶解し、これに酢酸アンモニウム 247mg を加え、室温で 24 時間撹拌した。反応液を留去し、得られた残渣をメタノール：水（２：９８）を溶出溶媒とするＯＤＳ（YMC-GEL ODS-A 120-230/70、以下同様）カラムクロマトグラフィーにて精製し、少量の１Ｎ塩酸を加えた後、再度留去し、Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－〔４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕フェニル〕メタンスルホンアミド　２塩酸塩 64mg を得た。

実施例１と同様にして表２の実施例２～３の化合物を得た。

実施例４

実施例２で得たエチル　〔Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－〔４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕フェニル〕スルファモイル〕アセテート　２塩酸塩 340mg を１，４－ジオキサン 10ml 及び水 10ml の混合液に溶解し、1Ｎ水酸化ナトリウム水溶液 3ml を加え室温で 3 時間撹拌した。１Ｎ塩酸 3ml を加え、反応液を留去した。得られた残渣をアセトニトリル：水（１０：９０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製し、少量の１Ｎ塩酸を加えた後、凍結乾燥し、〔Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－〔４－（４－ピリジル）ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル〕フェニル〕スルファモイル〕アセティックアシッド　２塩酸塩 154mg を得た。

実施例４と同様にして表２の実施例５、表４の実施例８５、表７の実施例９０～９３の化合物を得た。

実施例６

参考例２６で得たエチル　〔Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕スルファモイル〕アセテート 5.19g をクロロホルム 9ml 及びエタノール 9ml の混合液に溶解した。この溶液を撹拌下－20℃に冷却し、塩化水素を導入し飽和させた。この反応液を 5℃で 23 時間撹拌した後、反応液を留去した。得られた残渣をエタノール 18ml に溶解し、これに酢酸アンモニウム 6.6g を加え、室温で 28 時間撹拌した。反応液を留去し、得られた残渣をエタノール：水（１０：９０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製した。少量の１Ｎ塩酸を加え、凍結乾燥し、エチル　〔Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕スルファモイル〕アセテート　２塩酸塩 1.02g を得た。

実施例６と同様にして表２の実施例７～１５、表３の実施例４５～６３、表５の実施例８６の化合物を得た。

実施例１６

参考例２４で得たＮ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕メタンスルホンアミド 333mg をエタノール 10ml に溶解し、この溶液を撹拌下－20℃に冷却し、塩化水素を導入し飽和させた。この反応液を 5℃で 15 時間撹拌した後、反応液を留去した。得られた残渣をエタノール 10ml、メタノール 10ml の混合溶媒に溶解し、これに酢酸アンモニウム 480mg を加え、室温で 24 時間撹拌した。反応液を留去し、得られた残渣をＯＤＳカラムクロマトグラフィーにて精製した。メタノール：水（５：９５）で溶出される画分よりＮ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕スルホンアミドの粗精製物 249mg を得た。この粗精製物 224mg をエタノール 10ml に溶解し、エチルアセトイミデート塩酸塩 650mg とトリエチルアミン 683mg を加え室温で 20 時間撹拌した。反応液を留去後、得られた残渣をメタノール：水（５：９５）を溶出溶媒とするＯＤＳ（YMC-GEL ODS-A 120-230/70）カラムクロマトグラフィーにて精製した。１Ｎ塩酸を少量加えた後、凍結乾燥し、Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕メタンスルホンアミド　２塩酸塩 169mg を得た。

実施例１６と同様にして表２の実施例１７～２１、表３の実施例６４～６５の化合物を得た。

実施例２２

実施例６で得たエチル　〔Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕スルファモイル〕アセテート　２塩酸塩 590mg をエタノール 22ml に溶解し、エチルアセトイミデート塩酸塩 680mg とトリエチルアミン 555mg を加え室温で 15 時間撹拌した。反応液を留去し、得られた残渣をエタノール：水（１０：９０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製した。少量の１Ｎ塩酸を加えた後、凍結乾燥し、エチル　〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－ア

ミジノ－２－ナフチル）メチル〕スルファモイル〕アセテート　２塩酸塩 118mg を得た。

実施例２２と同様にして表２の実施例２３～２９、表３の実施例６６～７０、表４の実施例７１～７３、表５の実施例８７、表６の実施例８９の化合物を得た。

実施例３０

参考例２９で得たメチル　Ｎ－〔４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－シアノ－２－ナフチル）メチル〕マロナメート 1.37g をクロロホルム 15ml とメタノール 15ml の混合溶媒に溶解した後、この溶液を撹拌下－20℃に冷却し、塩化水素を導入し飽和させた。この反応液を 5℃で 21 時間撹拌した後、反応液を留去した。得られた残渣をメタノール 30ml に溶解し、これに酢酸アンモニウム 2.3g を加え、室温で３日間撹拌した。反応液を留去し、得られた残渣をメタノール：水（５：９５)を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製し、メチル　Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕マロナメートの粗精製物を得た。

この粗精製物をメタノール 30ml に溶解し、エチルアセトイミデート塩酸塩 5.56g とトリエチルアミン 4.45g を加え室温で２日間撹拌した。反応液を留去し、得られた残渣をメタノール：水（５：９５）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製した。１Ｎ塩酸を少量加えた後、凍結乾燥し、メチル　Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕マロナメート　２塩酸塩 950mg を得た。

実施例３１

実施例１１で得たエチル　〔Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕－Ｎ－〔４－（ヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－フルオロフェニル〕スルファモイル〕アセテート　２塩酸塩 980mg をエタノール 36ml に溶解し、エチルアセトイミデート塩酸塩 1.12g とトリエチルアミン 920mg を加え室温で５日間撹拌した。反応液を留去し、得られた残渣をエタノール：水

（１０：９０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製し、エチル　〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－フルオロフェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセテートの粗精製物を得た。この粗精製物 1.02g を濃塩酸 21ml に溶解し、室温で 16 時間撹拌した。反応液を留去し、得られた残渣を濃塩酸 20ml に溶解し、室温で 4 時間撹拌した。反応液を留去し、得られた残渣をアセトニトリル：水（５：９５）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製し、１Ｎ塩酸を少量加えた後、凍結乾燥し、〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－フルオロフェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセティックアシッド　２塩酸塩 940mg を得た。

実施例３１と同様にして表２の実施例３２の化合物を得た。

実施例３３

実施例２２で得たエチル　〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセテート　２塩酸塩 450mg を濃塩酸 8ml に溶解し、室温で 14 時間撹拌した。反応液を留去し、得られた残渣を濃塩酸 8ml に溶解し、室温で 4 時間撹拌した。反応液を留去し、得られた残渣をアセトニトリル：水（１０：９０）を溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製した。１Ｎ塩酸を少量加えた後、凍結乾燥し、〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセティックアシッド　２塩酸塩 302mg を得た。

実施例３３と同様にして表２の実施例３４、３５、表３の実施例３６～４２、表４の実施例７４～８４の化合物を得た。

実施例４３

実施例３１で得た〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－フルオロフェニル〕－Ｎ－〔（７－アミ

ジノー2－ナフチル）メチル〕スルファモイル〕アセティックアシッド　2塩酸塩 300mg をエタノール 10ml に溶解し、4 N塩酸ガスージオキサン溶液 1ml を加え、室温で 22 時間撹拌した。反応液を留去し、得られた残渣をエタノール 20ml に溶解し、4 N塩酸ガスージオキサン溶液 2ml を加え、室温で 7 時間撹拌した。反応液を留去し、得られた残渣をエタノールを溶出溶媒とするＯＤＳカラムクロマトグラフィーにて精製し、1 N塩酸を少量加えた後、凍結乾燥し、エチル　〔Ｎ－〔４－（４－アセトイミドイルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）－３－フルオロフェニル〕－Ｎ－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセテート　２塩酸塩 238mg を得た。

実施例４３と同様にして表３の実施例４４の化合物を得た。

実施例８８

参考例４０の化合物 538mg をピリジン 10ml、トリエチルアミン 2ml の混合溶媒に溶解し、0℃にて撹拌下硫化水素ガスを導入し飽和させた。この反応液を室温で 14 時間撹拌した後留去した。得られた残査を酢酸エチル：クロロホルム（１：２）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製しＮ－［４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル］－Ｎ－［（５－チオカルバモイル－２－ベンゾフラニル）メチル］メタンスルホンアミド 436mg を得た。得られた化合物 436mg をアセトン 9ml に溶解し、ヨウ化メチル 0.6ml を加え加熱還流下 1.5 時間撹拌した。溶媒を留去後、残査をメタノール 8ml に溶解し、酢酸アンモニウム 267mg を加え加熱還流下 1 時間撹拌した。溶媒を留去後、得られた残査をメタノール：クロロホルム（１：９）を溶出溶媒とするシリカゲルカラムクロマトグラフィーで精製した。得られたＮ－［４－（４－ｔ－ブトキシカルボニルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル)フェニル］－Ｎ－［（５－アミジノ－２－ベンゾフラニル）メチル］メタンスルホンアミドの粗精製物 412mg を 1,4-ジオキサン 16ml に溶解し、4 N塩化水素 1,4-ジオキサン溶液 8ml を加えた。反応溶液を室温で 40 分間撹拌した後溶媒を留去した。得られた残査をメタノール：水（５：９５）を溶出溶媒とする ODS カラムクロマトグラフィーで精製し 1N 塩酸を少量加えた後凍結乾燥しＮ－

［（５－アミジノ－２－ベンゾフラニル）メチル］－Ｎ－［４－（１Ｈ－１，４－ジアゼピン－１－イル）フェニル］メタンスルホンアミド三塩酸塩 108mg を得た。

実施例９４

Ｎ－［４－（４－メチルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル］－Ｎ－［（７－シアノ－２－ナフチル）メチル］スルファミド 230mg をエタノール 9.2ml に溶解し、これにトリエチルアミン 0.25ml とヒドロキシルアミン塩酸塩 90mg を加え２時間加熱環流した。反応液を留去後、得られた残査を濃アンモニア水、メタノール、クロロホルム（０．１：１：７）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにより精製した。溶媒を留去後、1N 塩酸水溶液を少量加え再度減圧留去し、Ｎ－［（７－ヒドロキシアミジノ－２－ナフチル）メチル］－Ｎ－［４－（４－メチルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル］スルファミド３塩酸塩 41mg を得た。

実施例９４と同様にして表７の実施例９５～１０１の化合物を得た。

実施例１０２

｛Ｎ－［（７－アミジノ－２－ナフチル）メチル］－Ｎ－［４－（４－メチルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル］｝スルファミド 210mg をジメチルスルホキシド 4ml に溶解し、これにトリエチルアミン 0.23ml とメチルクロロホルメート 0.042ml 室温で 50 分撹拌した。反応液に飽和炭酸水素ナトリウム水溶液を加えクロロホルムで抽出し、無水硫酸ナトリウムで乾燥した後、留去した。得られた残査を濃アンモニア水、メタノール、クロロホルム（０．１：１：１０）を溶出溶媒とするシリカゲルカラムクロマトグラフィーにより精製した。溶媒を留去後、希塩酸水溶液を少量加え凍結乾燥し、Ｎ－｛［７－（Ｎ－メトキシカルボニルアミジノ）－２－ナフチル］メチル｝－Ｎ－［４－（４－メチルヘキサヒドロ－１Ｈ－１，４－ジアゼピン－１－イル）フェニル］スルファミド３塩酸塩 121mg を得た。

実施例１０２と同様にして表７の実施例１０３～１０７の化合物を得た。

以下、表８～表１４に参考例化合物の構造及び物理化学的性状を、表２～表７

に実施例化合物の構造を、表１５～表２４に実施例化合物の物理化学的性状を示す。更に、表２５～表２７に構造を示す化合物は、前記実施例や製造法に記載の方法とほぼ同様にして、或いはそれらに当業者に自明の若干の変法を適用することにより容易に製造することが可能である。

なお、表中の記号は以下の意味を有する。

Rf.：参考例番号、 Ex.：実施例番号

NMR：核磁気共鳴スペクトル、 MS：質量分析値

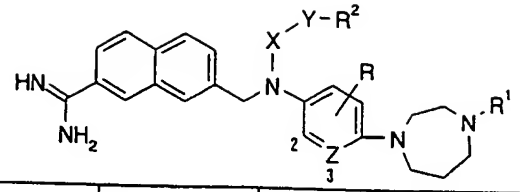
Me：メチル、 Et：エチル、 Py：ピリジル、 Bn：ベンジル、

nBu：ｎ－ブチル、 iPr：イソプロピル、 Boc：ブトキシカルボニル基

Tet：テトラゾリル基

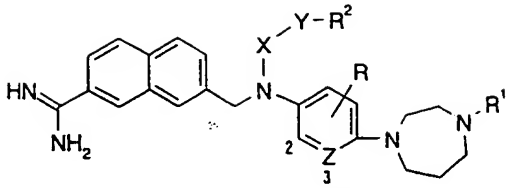
また、表中の置換基に付された「2-」及び「3-」は、化学名に関わらず、表中の構造式に付された「2」、「3」の位置に置換基が結合していることを意味するものとする。

表2



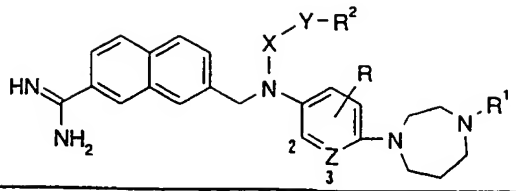
Ex	R^1	X	Y	R^2	Z	R	Sal
1	4-py	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
2	4-py	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
3	4-py	-CO-	$-CH_2CH_2-$	-COOMe	CH	H	2HCl
4	4-py	$-SO_2-$	$-CH_2-$	-COOH	N	H	2HCl
5	4-py	-CO-	$-CH_2-$	-COOH	CH	H	2HCl
6	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
7	H	$-SO_2NH-$	$-CH_2-$	-COOEt	CH	H	2HCl
8	H	-CO-	$-CH_2-$	-COOEt	CH	H	2HCl
9	H	-CO-	$-CH_2CH_2-$	-COOEt	CH	H	2HCl
10	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Me	2HCl
11	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-F	2HCl
12	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Cl	2HCl
13	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-Me	2HCl
14	H	$-SO_2-$	$-CH_2-$	-COOMe	CH	2-COOMe	2HCl
15	H	$-SO_2-$	$-CH_2-$	-COOEt	N	H	2HCl
16	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
17	-C(=NH)-Me	-CO-	$-CH_2-$	H	CH	H	2HCl
18	-C(=NH)-Me	$-SO_2NH-$	—	H	CH	H	2HCl
19	-C(=NH)-Me	$-SO_2NH-$	—	-COOEt	CH	H	2HCl
20	-C(=NH)-Me	-CONH-	$-CH_2-$	-COOEt	CH	H	2HCl
21	-C(=NH)-Me	-CONH-	—	-COOEt	CH	H	2HCl
22	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
23	-C(=NH)-Me	$-SO_2NH-$	$-CH_2-$	-COOEt	CH	H	2HCl
24	-C(=NH)-Me	-CO-	$-CH_2-$	-COOEt	CH	H	2HCl
25	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOEt	CH	H	2HCl
26	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	3-Me	2HCl
27	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Cl	2HCl
28	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-Me	2HCl
29	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOMe	CH	2-COOMe	2HCl
30	-C(=NH)-Me	-CO-	$-CH_2-$	-COOMe	CH	H	2HCl
31	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-F	2HCl
32	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	N	H	2HCl
33	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
34	-C(=NH)-Me	$-SO_2NH-$	$-CH_2-$	-COOH	CH	H	2HCl
35	-C(=NH)-Me	-CO-	$-CH_2-$	-COOH	CH	H	2HCl

表3



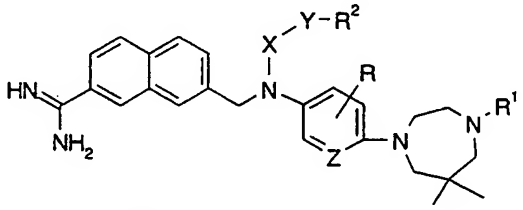
Ex	R^1	X	Y	R^2	Z	R	Sal
36	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOH	CH	H	2HCl
37	-C(=NH)-Me	-CONH-	$-CH_2-$	-COOH	CH	H	2HCl
38	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Me	2HCl
39	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	2-Me	2HCl
40	H	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
41	H	-CO-	$-CH_2-$	-COOH	CH	H	2HCl
42	H	-CO-	$-CH_2CH_2-$	-COOH	CH	H	2HCl
43	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	3-F	2HCl
44	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	N	H	2HCl
45	H	-CO-	$-CH_2-$	$-CONH_2$	CH	H	2HCl
46	H	-CO-	$-CH_2-$	-CONHMe	CH	H	2HCl
47	H	-CO-	$-CH_2-$	$-CON(Me)_2$	CH	H	2HCl
48	H	-CO-	—	-OEt	CH	H	2HCl
49	H	-CSNH-	$-CH_2-$	-COOEt	CH	H	2HCl
50	H	-CO-	$-CH_2-$	-Tet	CH	H	2HCl
51	-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
52	-Me	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
53	-Me	$-SO_2NH-$	—	-COOEt	CH	H	2HCl
54	-Me	$-SO_2NH-$	—	H	CH	H	2HCl
55	-Me	$-SO_2NH-$	$-CH_2-$	H	CH	H	2HCl
56	-Me	$-SO_2N(Me)-$	$-CH_2-$	H	CH	H	2HCl
57	-nBu	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
58	-Bn	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
59	$-C(=NH)-NH_2$	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
60	$-CH_2COOEt$	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
61	$-CH_2CONH_2$	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
62	H	-CO-	$-CH_2-$	-COOEt	N	H	2HCl
63	H	-CO-	$-CH_2CH_2-$	-COOEt	N	H	2HCl
64	-C(=NH)-Me	-CO-	$-CH_2-$	-COOnBu	CH	H	2HCl
65	-C(=NH)-Me	-CO-	$-CH_2-$	-COOiPr	CH	H	2HCl
66	-C(=NH)-Me	-CO-	$-CH_2-$	$-CONH_2$	CH	H	2HCl
67	-C(=NH)-Me	-CO-	$-CH_2-$	-CONHMe	CH	H	2HCl
68	-C(=NH)-Me	-CO-	$-CH_2-$	$-CON(Me)_2$	CH	H	2HCl
69	-C(=NH)-Me	-CO-	—	-OEt	CH	H	2HCl
70	-C(=NH)-Me	-CSNH-	$-CH_2-$	-COOEt	CH	H	2HCl

表4



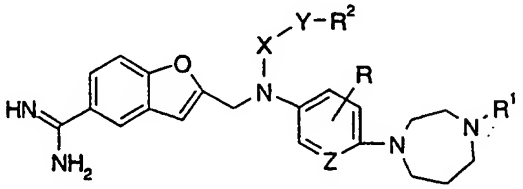
Ex	R^1	X	Y	R^2	Z	R	Sal
71	-C(=NH)-Me	-CO-	$-CH_2-$	-Tet	CH	H	2HCl
72	-C(=NH)-Me	-CO-	$-CH_2-$	-COOEt	N	H	2HCl
73	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOEt	N	H	2HCl
74	H	-CSNH-	$-CH_2-$	-COOH	CH	H	2HCl
75	-C(=NH)-Me	-CSNH-	$-CH_2-$	-COOH	CH	H	2HCl
76	-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
77	-nBu	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
78	-Bn	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
79	$-C(=NH)-NH_2$	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
80	H	$-SO_2-$	$-CH_2-$	-COOH	N	H	2HCl
81	H	-CO-	$-CH_2-$	-COOH	N	H	2HCl
82	-C(=NH)-Me	-CO-	$-CH_2-$	-COOH	N	H	2HCl
83	H	-CO-	$-CH_2CH_2-$	-COOH	N	H	2HCl
84	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOH	N	H	2HCl
85	$-CH_2COOH$	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl

表5



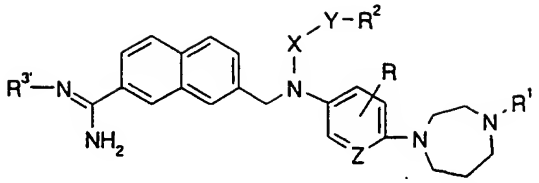
Ex.	R^1	X	Y	R^2	Z	R	Sal
86	H	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
87	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl

表6



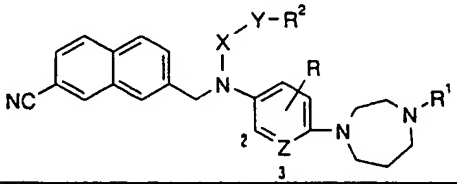
Ex.	R^1	X	Y	R^2	Z	R	Sal
88	H	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
89	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl

表7



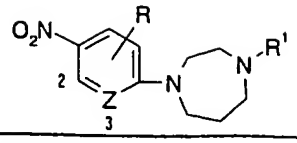
Ex.	$R^{3'}$	R^1	X	Y	R^2	Z	R	Sal
90	-OH	4-Py	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
91	-OH	-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
92	-COOMe	-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
93	-OH	H	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
94	-OH	-Me	$-SO_2NH-$	—	H	CH	H	3HCl
95	-OH	4-Py	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
96	-OH	-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
97	-OH	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
98	-OH	-Me	$-SO_2NH-$	$-CH_2-$	H	CH	H	3HCl
99	-OH	-Me	$-SO_2N(Me)-$	$-CH_2-$	H	CH	H	3HCl
100	-OH	-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
101	-OH	-Me	$-SO_2NH-$	—	-COOEt	CH	H	3HCl
102	-COOMe	-Me	$-SO_2NH-$	—	H	CH	H	3HCl
103	-COOMe	-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
104	-COOMe	-Me	$-SO_2NH-$	$-CH_2-$	H	CH	H	3HCl
105	-COOMe	-Me	$-SO_2N(Me)-$	$-CH_2-$	H	CH	H	3HCl
106	-COOMe	-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
107	-COOMe	-Me	$-SO_2NH-$	—	-COOEt	CH	H	3HCl

表8



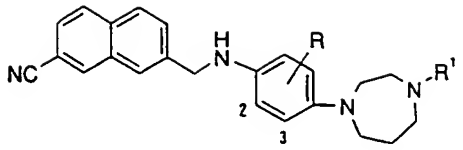
Rf	R^1	X	Y	R^2	Z	R	Rf.	R^1	X	Y	R^2	Z	R
4	3-py	$-SO_2-$	$-CH_2-$	H	CH	H	24	-Boc	$-SO_2-$	—	Me	CH	H
5	3-py	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	25	-Boc	-CO-	—	Me	CH	H
6	3-py	-CO-	$-CH_2-$	-COOMe	CH	H	27	-Boc	$-SO_2NH-$	—	-Boc	CH	H
26	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	28	-Boc	$-SO_2NH-$	—	-COOEt	CH	H
29	-Boc	-CO-	$-CH_2-$	-COOMe	CH	H	30	-Boc	-CONH-	$-(CH_2)_2-$	-COOEt	CH	H
32	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Me	31	-Boc	-CONH-	$-CH_2-$	-COOEt	CH	H
33	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Cl	36	-Boc	-CONH-	—	-COOEt	CH	H
34	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-Me	38	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	N	H
35	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-COOMe	39	-Boc	$-SO_2N$(Boc)-	$-CH_2-$	-COOEt	H	H
37	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-F							

表 9



Rf.	R'	Z	R^3	DATA
1	H	CH	H	NMR(DMSO-d6) δ :2.07-2.18(2H,m),3.18-3.29(4H,m),3.67(2H,t, J=5.9Hz),3.90(2H,t,J=5.9Hz),6.92(2H,d,J=9.5Hz),8.09(2H,d,J=9 .5Hz),9.32(3H,br)
2	3-Py	CH	H	NMR($CDCl_3$) δ :2.02-2.21(2H,m),3.42-3.70(8H,m),6.55(2H,d,J=3.2 Hz),6.69(2H,d,J=9.5Hz),8.14(2H,d,J=9.5Hz),8.26(2H,d,J=3.2Hz)
7	H	CH	3-Me	NMR($CDCl_3$) δ :1.89-1.97(2H,m),2.38(3H,s),2.82-3.08(4H,m),3.35-3.73(4H,m),6.99(1H,d,J=8.9Hz),7.97-8.00(1H,m),8.61(1H,br)
8	H	CH	3-Cl	NMR($CDCl_3$) δ :1.93-2.03(2H,m),3.03(2H,t,J=5.8Hz),3.03(2H,t,J= 5.8Hz),3.53-3.61(4H,m),7.01(1H,d,J=9.1Hz),8.01(1H,dd, J=9.1Hz),8.20(1H,dd,J=2.9Hz)
9	H	CH	2-Me	NMR($CDCl_3$) δ :1.86-1.94(2H,m),2.64(3H,s),2.83(2H,t,J=5.6Hz), 3.04(2H,t,J=5.6Hz),3.61(2H,t,J=5.6Hz),3.66(2H,t,J=5.6Hz),6.44 (1H,d,J=2.8Hz),6.52(1H,dd,J=2.8Hz,9.4Hz),8.09(1H,d,J=9.4Hz)
10	H	CH	2-CN	NMR($CDCl_3$) δ :1.84-2.05(2H,m),2.87(2H,t,J=5.4Hz),3.07(2H,t, J=5.4Hz),3.58-3.77(4H,m),6.81(1H,dd,J=2.9Hz,9.5Hz),6.97 (1H,d,J=2.9Hz),8.18(1H,d,J=9.5Hz)
11	H	CH	2-COOMe	NMR($CDCl_3$) δ :1.79-1.83(2H,m),2.74(2H,t,J=5.5Hz),2.95(2H,t, J=5.5Hz),3.50-3.59(4H,m),3.84(3H,s),6.56(1H,s),7.17(1H,d, J=8.2Hz),7.91(1H,d,J=8.2Hz)
12	Boc	CH	H	NMR($CDCl_3$) δ :1.40(9H,s),1.85-2.10(2H,m),3.19-3.35(2H,m),3.58-3.72(6H,m),6.71(2H,d,J=9.5Hz),8.12(2H,d,J=9.5Hz)
13	Boc	CH	3-F	NMR($CDCl_3$) δ :1.36(4H,s),1.43(5H,s),1.91-2.02(2H,m),3.35-3.48 (2H,m),3.59-3.72(6H,m),6.75-6.81(1H,m),7.86-7.95(2H,m)
14	Boc	N	H	NMR($CDCl_3$) δ :1.42(9H,s),1.80-2.09(2H,m),3.07-3.55(8H,m),4.47 (2H,s),6.61(4H,s),7.50-7.71(2H,m),7.82-7.94(3H,m),8.17(1H,s)
15	Boc	CH	3-Me	NMR($CDCl_3$) δ :1.52(9H,s),1.92-2.05(2H,m),2.37(3H,s),3.17-3.31 (4H,m),3.57-3.67(4H,m),7.02(1H,d,J=8.8Hz),7.96-8.04(2H,m)
16	Boc	CH	3-Cl	NMR($CDCl_3$) δ :1.53(9H,s),2.01-2.12(2H,m),3.39-3.49(2H,m),3.51-3.70(4H,m),7.05(1H,d,J=9.0Hz),8.03(1H,dd,2.5Hz,9.0Hz),8.24 (1H,d,J=2.5Hz)
17	Boc	CH	2-Me	NMR($CDCl_3$) δ :1.53(9H,s),1.94-2.02(2H,m),2.64(3H,s),3.23-3.38 (2H,m),3.59-3.66(6H,m),6.45(1H,d,J=2.5Hz),6.54(1H,dd, J=2.5Hz,9.1Hz),8.10(1H,d,J=9.1Hz)
18	Boc	CH	2-COOMe	NMR($CDCl_3$) δ :1.42(9H,s),1.91-2.02(2H,m),3.24-3.40(2H,m),3.58-3.70(6H,m),3.93(3H,s),6.64-6.74(2H,m),8.03(1H,d,J=9.1Hz)
21-1	Bn	CH	3-Cl	NMR($CDCl_3$) δ :1.98-2.06(2H,m),2.76(2H,d,J=5.5Hz),2.84(2H,t, J=5.1Hz),3.55-3.66(4H,m),3.67(2H,s),6.94(1H,d,J=9.2Hz),7.23-7.38(5H,m),8.01(1H,dd,J=3.0Hz,9.2Hz),8.21(1H,d,J=2.9Hz)

表10



Rf.	R_1	R_3	DATA
3	3-Py	H	NMR($CDCl_3$) δ :2.05-2.16(2H,m),3.35-3.48(4H,m), 3.51-3.58(2H,m),3.63-3.68(2H,m),4.48(2H,s), 6.52-6.58(2H,m),6.79(1H,d,J=8.9Hz),7.35(1H,d, J=8.9Hz),7.56-7.60(1H,m),7.63-7.69(2H,m),7.86-7.90(2H,m),8.20-8.27 (2H,m),8.70(1H,s)
19	Boc	H	NMR($CDCl_3$) δ :1.40(4H,s),1.42(5H,s),1.94-2.00(2H,m), 3.27-3.40(2H,m), 3.57-3.62(2H,m),3.71-3.93(4H,m), 6.50(1H,d,J=9.5Hz),8.20 (1H,dd,J=2.6Hz,9.5Hz),9.04(1H,d,J=2.6Hz)
20	Boc	3-Me	NMR($CDCl_3$) δ :1.45(4H,s),1.48(5H,s),1.82-1.95(2H,m), 2.23(3H,s),2.91-3.02(4H,m),3.44-3.59(4H,m),4.69(2H,s),6.41-6.46(1H,m),6.51(1H,s), 6.87(1H,d,J=8.5Hz),7.77(1H,dd,J=1.8Hz,8.4Hz),7.62-7.66(1H,m), 7.83-7.88(3H,m),8.16(1H,s)
21-2	Bn	3-Cl	NMR($CDCl_3$) δ :1.88-1.95(2H,m),2.70-2.82(4H,m),3.13-3.21(4H,m),3.69 (2H,s),4.48(2H,d,J=5.5Hz),6.48(1H,dd,J=2.9Hz,8.8Hz),6.68(1H,d, J=3.0Hz), 6.97(1H,d,J=8.8Hz),7.31-7.37(5H,m),7.58(1H,dd,J=1.8Hz, 8.4Hz),7.62(1H,dd,J=1.8Hz,8.8Hz),7.84-7.91(3H,m),8.18(1H,s)
21-3	Boc	3-Cl	NMR($CDCl_3$) δ :1.47(9H,s),1.91-2.00(2H,m),3.09-3.11(4H,m),3.56-3.61 (4H,m),4.49(2H,d,J=4.8Hz),6.47(1H,dd,J=2.5Hz,8.2Hz),6.68(1H,d,J= 2.5Hz),6.92(1H,d,J=8.2Hz),7.57-7.64(2H,m),7.84-7.92(3H,m),8.19(1H,s)
22	Boc	2-Me	NMR($CDCl_3$) δ :1.31(4H,s),1.44(5H,s),1.90-2.01(2H,m),2.21(3H,s),3.18-3.34(2H,m),3.40-3.58(6H,m),4.50(2H,s), 6.44-6.58(3H,m),7.58(1H,dd, J=1.9Hz,8.4Hz),7.68(1H,dd,J=1.9Hz,8.4Hz),7.84-7.92(3H,m),8.19(1H,s)
23	Boc	2-COOMe	NMR($CDCl_3$) δ :1.35(4H,s),1.49(5H,s),1.87-2.01(2H,m), 3.20-3.34(2H,m), 3.40-3.49(4H,m),3.51-3.58(2H,m),3.89(3H,s),4.61(2H,d,J=5.5Hz),6.55 (1H,d,J=9.1Hz), 6.82(1H,dd,J=2.5Hz,9.1Hz),7.32(1H,d,J=2.5Hz),7.57 (1H,dd,J=1.6Hz,8.5Hz),7.65(1H,dd,J=1.6Hz,8.5Hz),7.76-7.86(3H,m), 8.17(1H,s)

表11

Rf.	DATA
4	NMR($CDCl_3$) δ :1.92-2.25(2H,m),2.98(3H,s),3.30-3.58(8H,m),4.95(2H,s),6.40-6.68(4H,m),7.08 (2H,d,J=9.0Hz),7.56-7.88(4H,m),8.07-8.30(4H,m)
5	NMR($CDCl_3$) δ :1.39(3H,t,J=7.2Hz),2.01-2.07(2H,m),3.38-3.43(4H,m),3.57-3.64(4H,m),4.06 (2H,s),4.35(2H,q,J=7.2Hz),5.02(2H,s),6.50-6.52(2H,m),6.58(2H,d,J=8.8Hz),7.21 (2H,d,J=8.8Hz),7.57(1H,dd,J=1.6Hz,8.4Hz),7.83(1H,d,J=8.4Hz),7.87(1H,d,J=8.4Hz), 8.12(1H,s),8.20-8.22(2H,m)
6	NMR($CDCl_3$) δ :2.02(2H,m),3.29(2H,s),3.40-3.47(4H,m),3.61-3.66(4H,m),3.70(3H,s),5.03 (2H,s),6.52(2H,d,J=6.4Hz),6.57(2H,d,J=8.8Hz),6.83(2H,d,J=8.8Hz),7.59 (1H,dd,J=1.6Hz,8.4Hz),7.64(1H,dd,J=1.6Hz,8.4Hz),7.70(1H,s),7.84(1H,d,J=8.4Hz),7.89 (1H,d,J=8.4Hz),m),8.15(1H,s),8.22(2H,d,J=6.4Hz)
24	NMR($CDCl_3$) δ :1.30(4H,s),1.38(5H,s),1.84-1.94(2H,m),2.97(3H,s), 3.15-3.33(2H,m),3.44-3.56 (6H,m),4.94(2H,s),6.55(2H,d,J=9.2Hz),7.02-7.10(2H,m),7.58(1H,dd,J=1.9Hz,8.4Hz), 7.65-7.73(2H,m),7.84(1H,d,J=9.9Hz),7.84(1H,d,J=9.9Hz),8.13(1H,s)

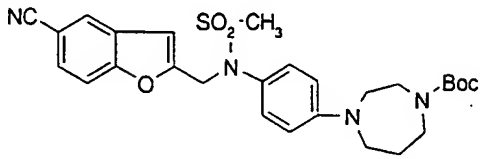
表12

Rf.	DATA
25	NMR($CDCl_3$) δ :1.35(4H,s),1.40(5H,s),1.85-1.96(5H,m),3.19-3.37(2H,m),3.47-3.58(6H,m),5.00 (2H,s),6.57(2H,d,J=9.2Hz),6.75-6.82(2H,m),7.55-7.67(3H,m),7.82(1H,d,J=8.6Hz), 7.88(1H,d,J=8.6Hz),8.15(1H,s)
26	NMR($CDCl_3$) δ :1.26(3H,t,J=7.3Hz),1.31(4H,s),1.39(5H,s),1.75-2.01(2H,m),3.13-3.31(2H,m), 3.45-3.57(6H,m),4.04(2H,s),4.35(2H,q,J=7.3Hz),5.02(2H,s),6.55(2H,d,J=9.0Hz),7.20 (2H,d,J=9.0Hz),7.50-7.92(5H,m),8.13(1H,s)
27	NMR($CDCl_3$) δ :1.29(9H,s),1.43(9H,s),1.79-1.88(2H,m),3.16-3.32(2H,m),3.46-3.53(6H,m), 5.19(2H,s),6.54(2H,d,J=9.0Hz),7.04-7.11(2H,m), 7.57(1H,dd,J=1.9Hz,9.0Hz), 7.65-7.70(2H,m),7.81-7.89(2H,m),8.13(1H,s)
28	NMR($CDCl_3$) δ :1.30(4H,s),1.37(3H,t,J=7.0Hz),1.39(5H,s),1.84-1.91(2H,m),3.15-3.21(1.4H,m) ,3.25-3.30(0.6H,m),3.44-3.51(6H,m),4.33(2H,q,J=7.0Hz),5.19(2H,s),6.54(2H,d,J=9.2Hz), 7.04-7.07(2H,m),7.57(1H,dd,J=1.4Hz,8.4Hz),7.65-7.70(2H,m),7.84(1H,d,J=8.4Hz), 7.87(1H,d,J=8.8Hz),8.13(1H,s),8.56-8.61(1H,m)
29	NMR($CDCl_3$) δ :1.35(4H,s),1.40(5H,s),1.86-1.92(2H,m),3.18-3.35(4H,m),3.47-3.55(6H,m),3.70 (3H,s),5.03(2H,s),6.55(2H,d,J=8.8Hz),6.79-6.85(2H,m),7.58(1H,dd,J=1.4Hz,8.4Hz),7.64 (1H,dd,J=1.4Hz,8.4Hz), 7.70(1H,s),7.84(1H,d,J=8.4Hz),7.86(1H,d,J=8.4Hz),8.15(1H,s)
30	NMR($CDCl_3$) δ :1.26(3H,t,J=7.4Hz),1.35(4H,s),1.41(5H,s),1.86-1.95(2H,m),2.40(2H,t,J=6.6Hz),2.64(2H,t,J=6.6Hz),3.20-3.26(1H,m),3.29-3.35(1H,m),3.47-3.56(6H,m),4.15(2H,q,J=7.4 Hz),5.00(2H,s),6.57(2H,d,J=8.8Hz), 6.63-6.68(2H,m),7.58(1H,dd,J=1.5Hz,8.5Hz),7.59(1H, dd,J=1.5Hz,8.5Hz),7.69(1H,s),7.82(1H,d,J=8.5Hz),7.88(1H,d,J=8.5Hz),8.15(1H,s)
31	NMR($CDCl_3$) δ :1.27(3H,t,J=7.2Hz),1.34(4H,s),1.40(5H,s),1.84-1.97(2H,m),3.17-3.35(2H,m), 3.45-3.57(6H,m),3.98(2H,d,J=6.0Hz),4.18(2H,q,J=7.2Hz),4.85(1H,t,J=6.0Hz),4.98(2H,s), 6.59(2H,d,J=9.0Hz),6.90-7.00(2H,m), 7.56(1H,dd,J=1.5Hz,8.4Hz),7.65(1H,d,J=9Hz), 7.69(1H,s),7.82(1H,d,J=8.4Hz),7.87(1H,d,J=8.4Hz),8.15(1H,s)
32	NMR($CDCl_3$) δ :1.38(3H,t,J=7.3Hz),1.45(5H,s),1.47(4H,s),1.84-1.96(2H,m),2.21(3H,s),2.94-3.06(4H,m),3.47-3.60(4H,m),3.93(2H,s),4.34(2H,q,J=7.3Hz),5.04(2H,s),6.92(2H,d,J=8.5Hz),7.13-7.18(3H,m),7.56-7.61(1H,m),7.82-7.88(2H,m),8.12(1H,s)
33	NMR($CDCl_3$) δ :1.38(3H,t,J=7.2Hz),1.45(9H,br),1.92-2.02(2H,m),3.08-3.14(4H,m),3.49-3.61 (4H,m),4.04(2H,s),4.35(2H,q,J=7.2Hz),5.03(2H,s),6.94(1H,d,J=8.5Hz),7.17(1H,dd,J=2.2Hz ,8.5Hz),7.43-7.47(2H,m),7.57(1H,dd,J=1.5Hz,8.5Hz),7.64-7.68(1H,m),7.827.90(2H,m), 8.14(1H,s)
34	NMR($CDCl_3$) δ :1.39-1.42(12H,m),1.78(3H,s),1.86-1.95(2H,m),3.18-3.27(2H,m),3.45-3.56 (6H,m),4.00(1H,d,J=14Hz),4.18(1H,d,J=14Hz),4.34(2H,q,J=7.0Hz),4.62(1H,d,J=14Hz), 5.19(1H,d,J=14Hz),6.34(1H,d,J=2.7Hz),6.54(1H,d,J=2.7Hz,8.8Hz),7.55-7.61(2H,m),7.67 (1H,dd,J=1.5Hz,8.4Hz),7.69(1H,d,J=1.5Hz),7.82(1H,d,J=8.4Hz),7.88(1H,d,J=8.4Hz), 8.10(1H,s)
35	NMR($CDCl_3$) δ :1.29-1.36(7H,m),1.41(5H,s),1.86-1.94(2H,m),3.17-3.32(2H,m),3.46-3.54 (6H,m),3.83(3H,s),4.08(2H,d,J=15.8Hz),4.26(2H,q,J=7.0Hz),4.82(1H,br),5.24(1H,br),6.59 (1H,dd,J=3.3Hz,8.8Hz),6.96-7.02(2H,m),7.10(1H,d,J=3.3Hz),7.58(1H,dd,J=1.4Hz,8.4Hz), 7.68-7.73(1H,m),7.82(1H,d,J=8.5Hz),7.88(1H,d,J=8.5Hz),8.12(1H,s)
36	NMR($CDCl_3$) δ :1.26(3H,t,J=7.2Hz),1.36(4H,s),1.41(5H,s),1.85-1.97(2H,m),3.22-3.38(2H,m), 3.47-3.60(6H,m),4.19(2H,q,J=7.2Hz),4.96(2H,s),6.61(2H,d,J=9.0Hz),6.77(1H,s),6.83(2H,d, J=8.4Hz),7.58(1H,dd,J=1.8Hz,8.4Hz),7.63-7.70(2H,m),7.83(1H,d,J=9.0Hz),7.89(1H,d, J=8.4Hz),8.14(1H,s)
37	NMR($CDCl_3$) δ :1.34(4H,s),1.39(3H,t,J=7.4Hz),1.40(5H,s),1.83-1.94(2H,m),3.32-3.45(6H,m), 3.49-3.57(2H,m),4.04(2H,s),4.35(2H,q,J=7.4Hz),5.01(2H,s),6.68-6.75(1H,m),7.00-7.10 (2H,m),7.58(1H,dd,J=1.9Hz,8.5Hz),7.64-7.68(2H,m),7.84(1H,d,J=8.4Hz),7.87(1H,d,J=8.4 Hz),8.14(1H,s)

表13

Rf.	DATA
38	NMR($CDCl_3$) δ :1.34-1.41(12H,m),1.84-1.91(2H,m),3.20-3.34(2H,m),3.48-3.61(4H,m),3.68-3.72(2H,m),4.06(2H,s),4.35(2H,q,J=6.9Hz),5.00(2H,s),6.36(1H,d,J=9.2Hz),7.27-7.39(1H,m),7.58(1H,dd,J=1.7Hz,8.6Hz),7.65-7.70(2H,m),7.85(1H,d,J=8.1Hz),7.88(1H,d,J=8.1Hz),8.13-8.15(2H,m)
39	NMR($CDCl_3$) δ :1.24(3H,t,J=7.2Hz),1.30(9H,s),1.38(9H,s),1.82-1.94(2H,m),3.14-3.31(2H,m),3.44-3.54(6H,m),4.08(2H,s),4.16(2H,q,J=7.2Hz),5.16(2H,s),6.52(2H,d,J=9.0Hz),7.01-7.07(2H,m),7.56(1H,dd,J=1.9Hz,9.0Hz),7.65-7.70(2H,m),7.81-7.89(2H,m),8.12(1H,s)

表14



Rf.	DATA
40	NMR($CDCl_3$) δ :1.35(s,4H),1.41(s,5H),1.87-1.97(m,2H),2.98(s,3H),3.18-3.27(m,1H),3.27-3.36(m,1H),3.48-3.60(m,6H),4.93(s,2H),6.60(d,2H,J=9.0Hz),6.65(s,1H),7.08(d,2H,J=9.0Hz),7.54-7.57(m,2H),7.85(s,1H)

表15

Ex	DATA
1	NMR(DMSO-d_6) δ :1.80-1.90(2H,m),3.05(3H,s),3.42-3.46(2H,m),3.56-3.63(2H,m),3.85-3.90(4H,m),4.97(2H,s),6.66(2H,d,J=9.2Hz),7.02-7.11(2H,m),7.15(2H,d,J=9.2Hz),7.62(1H,dd,J=1.9Hz,8.8Hz),7.79(1H,dd,J=1.9Hz,8.8Hz),7.91(1H,s),8.00(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.12-8.17(2H,m),8.46(1H,s),9.19(3H,br),9.46(2H,br)
2	NMR(DMSO-d_6) δ :1.27(3H,t,J=6.8Hz),1.82-1.89(2H,m),3.42-3.46(2H,m),3.60-3.63(4H,m),3.83-3.86(2H,m),4.24(2H,q,J=6.8Hz),4.33(2H,s),4.98(2H,s),6.82(2H,d,J=9.2Hz),7.03-7.10(2H,m),7.15(2H,d,J=9.2Hz),7.60(1H,dd,J=1.6Hz,8.8Hz),7.82(1H,dd,J=1.6Hz,8.8Hz),7.89(1H,s),8.01(1H,d,J=8.8Hz),8.11(1H,d,J=8.8Hz),8.12-8.16(2H,m),8.48(1H,s),9.31(2H,s),9.52(2H,s),13.68(1H,br)
3	NMR(DMSO-d_6) δ :1.81-1.88(2H,m),3.21(2H,s),3.44-3.47(2H,m),3.57(3H,s),3.60-3.66(4H,m),3.84-3.86(2H,m),4.99(2H,s),6.69(2H,d,J=9.2Hz),6.93(2H,d,J=9.2Hz),7.02-7.10(2H,m),7.57(1H,dd,J=1.6Hz,8.4Hz),7.82(1H,dd,J=1.6Hz,8.4Hz),7.87(1H,s),8.02(1H,d,J=8.4Hz),8.12(1H,d,J=8.4Hz),8.13-8.17(2H,m),8.45(1H,s),9.29(2H,s),9.53(2H,s),13.66(1H,br)
4	NMR(DMSO-d_6) δ :1.83-1.89(2H,m),3.42-3.45(2H,m),3.59-3.63(4H,m),3.83-3.86(2H,m),4.22(2H,s),4.98(2H,s),6.69(2H,d,J=8.8Hz),7.03-7.09(2H,m),7.15(2H,d,J=8.8Hz),7.61(1H,dd,J=1.6Hz,8.4Hz),7.83(1H,dd,J=1.6Hz,8.4Hz),7.89(1H,s),8.01(1H,d,J=8.4Hz),8.11(1H,d,J=8.4Hz),8.12-8.15(2H,m),8.50(1H,s),9.37(2H,s),9.55(2H,s),13.76(1H,br)
5	NMR(DMSO-d_6) δ :1.82-1.89(2H,m),3.12(2H,s),3.45-3.48(2H,m),3.60-3.66(4H,m),3.84-3.87(2H,m),4.99(2H,s),6.70(2H,d,J=8.8Hz),6.95(2H,d,J=8.8Hz),7.02-7.09(2H,m),7.58(1H,dd,J=1.6Hz,8.4Hz),7.84(1H,dd,J=1.6Hz,8.4Hz),7.90(1H,s),8.02(1H,d,J=8.8Hz),8.11-8.16(3H,m),8.48(1H,s),9.39(2H,s),9.58(2H,s),13.80(1H,br)
6	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.0Hz),2.01-2.07(2H,m),3.03-3.06(2H,m),3.11-3.15(2H,m),3.41(2H,t,J=6.0Hz),3.62-3.65(2H,m),4.24(2H,q,J=7.0Hz),4.36(2H,s),5.01(2H,s),6.68(2H,d,J=9.2Hz),7.20(2H,d,J=9.2Hz),7.66(1H,dd,J=1.7Hz,8.6Hz),7.82(1H,dd,J=1.7Hz,8.6Hz),7.90(1H,s),8.02(1H,d,J=8.6Hz),8.10(1H,d,J=8.6Hz),8.49(1H,s),9.27(2H,br),9.31(2H,s),9.52(2H,s)

表16

Ex	DATA
7	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.0Hz),2.01-2.08(2H,m),2.99-3.06(2H,m),3.08-3.15(2H,m), 3.34-3.42(2H,m),3.59-3.65(2H,m),3.81(2H,d,J=5.2Hz),4.18(2H,q,J=7.0Hz),4.91(2H,s),6.63 (2H,d,J=9.0Hz),7.16(2H,d,J=9.0Hz),7.66(1H,dd,J=1.5Hz,8.4Hz),7.81(1H,dd,J=1.5Hz, 8.4Hz),7.88(1H,s),7.96-8.01(2H,m),8.08(1H,d,J=8.8Hz),8.45(1H,s),9.42(4H,br),9.53(2H,br)
8	NMR(DMSO-d_6) δ :1.16(3H,t,J=7.0Hz),2.02-2.09(2H,m),3.01-3.06(2H,m),3.10-3.15(2H,m), 3.28(2H,s),3.43(2H,t,J=7.0Hz),3.63-3.67(2H,m),4.04(2H,q,J=7.0Hz),5.03(2H,s),6.69(2H,d, J=9.1Hz),7.00(2H,d,J=9.1Hz),7.63(1H,dd,J=1.6Hz,9.6Hz),7.81(1H,dd,J=1.6Hz,8.6Hz),7.87 (1H,s),8.04(1H,d,J=8.6Hz),8.12(1H,d,J=8.6Hz),8.45(1H,s),9.29(4H,s),9.53(2H,s)
9	NMR(DMSO-d_5) δ :1.18(3H,t,J=7.0Hz),1.89-1.96(2H,m),2.35(2H,t,J=7.0Hz),2.53(2H,t, J=7.0Hz),2.89(2H,t,J=5.6Hz),3.02(2H,t,J=5.2Hz),3.44(2H,t,J=6.2Hz),3.56(2H,t,J=5.2Hz), 4.06(2H,q,J=7.0Hz),4.99(2H,s),6.67(2H,d,J=9.2Hz),6.99(2H,d,J=9.2Hz),7.61(1H,dd, J=1.6Hz, 8.2Hz),7.79(1H,dd,J=1.6Hz,8.2Hz),7.84(1H,s),8.01(1H,d,J=8.6Hz),8.11(1H,d, J=8.6Hz),8.44(1H,s),9.52(6H,br)
10	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),1.95-2.04(2H,m),2.21(3H,s),3.02(2H,t,J=5.5Hz), 3.16-3.26(6H,m),4.23(2H,q,J=7.0Hz),4.41(2H,s),5.06(2H,s),7.02(1H,d,J=8.8Hz),7.17 (1H,dd,J=2.4Hz,8.8Hz),7.28(1H,d,J=2.4Hz), 7.64-7.68(1H,m),7.80-7.84(1H,m),7.93(1H,s), 8.02(1H,d,J=8.5Hz),8.10(1H,d,J=8.5Hz),8.49(1H,s),9.34(2H,br),9.41(2H,br),9.54(2H,br)
11	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),2.03-2.10(2H,m),3.13-3.22(4H,m),3.27(2H,t,J=6.8Hz), 3.42-3.46(2H,m),4.23(2H,q,J=7.0Hz),4.45(2H,s),5.06(2H,s),6.84-6.89(1H,m),7.11(1H,dd, J=2.8Hz,9.2Hz),7.28(1H,dd,J=2.8Hz,14.4Hz),7.66(1H,dd,J=1.6Hz,8.8Hz),7.80(1H,dd, J=1.6Hz,8.8Hz),7.94(1H,s),8.02(1H,d,J=8.8Hz), 8.10(1H,d,J=8.8Hz),8.48(1H,s),9.15 (2H,br),9.23(2H,s),9.49(2H,s)
12	NMR(DMSO-d_5) δ :1.24(3H,t,J=7.3Hz),2.00-2.03(2H,m),3.14-3.28(6H,m),3.31-3.36(2H,m), 4.23(2H,q,J=7.3Hz),4.50(2H,s),5.04(2H,s),7.14(1H,d,J=8.8Hz),7.32(1H,dd,J=2.3Hz,8.8Hz) ,7.53(1H,d,J=2.3Hz),7.64-7.68(1H,m),7.82(1H,dd,J=1.9Hz,8.5Hz),7.94(1H,s),8.03(1H,d, J=8.5Hz),8.10(1H,d,J=8.5Hz),8.49(1H,s),9.32(4H,br),9.51(2H,br)
13	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),1.83(3H,s),2.02-2.10(2H,m),3.01-3.09(2H,m),3.11-3.17 (2H,m),3.40-3.46(2H,m),3.63-3.71(2H,m),4.24(2H,q,J=7.0Hz),4.32(1H,d,J=14.3Hz),4.52 (1H,d,J=14.3Hz),4.68(1H,d,J=14.3Hz),5.12(1H,d,J=14.3Hz),6.47(1H,d,J=2.7Hz),6.65(1H, dd,J=2.7Hz,8.8Hz),7.38(1H,d,J=8.8Hz),7.64(1H,dd,J=1.6Hz,8.4Hz),7.80(1H,s),7.84(1H,dd, J=1.6Hz,8.4Hz),8.02(1H,d,J=8.4Hz),8.11(1H,d,J=8.4Hz),8.47(1H,s),9.40(4H,br),9.55 (2H,br)
14	NMR(DMSO-d_6) δ :2.01-2.09(2H,m),3.03-3.10(2H,m),3.11-3.19(2H,m),3.41-3.48(2H,m),3.65-3.70(2H,m),3.71(3H,s),3.72(3H,s),4.39(2H,d,J=4.8Hz),4.97(2H,br),6.85(1H,dd,J=2.9Hz,8.8 Hz),6.97(1H,d,J=2.9Hz),7.19(1H,d,J=8.8Hz), 7.71(1H,dd,J=1.5Hz,8.4Hz),7.82(1H,dd,J=1.5 Hz,8.4Hz),7.88(1H,s),8.01(1H,d,J=8.4Hz),8.10(1H,d,J=8.4Hz),8.45(1H,s),9.28(4H,br),9.52 (2H,br)
15	NMR(DMSO-d_5) δ :1.27(3H,t,J=7.2Hz),1.92-2.04(2H,m),3.08-3.18(4H,m),3.56-3.61(2H,m), 3.81-3.85(2H,m),4.24(2H,q,J=7.2Hz),4.47(2H,s),5.04(2H,s),6.68(1H,d,J=8.8Hz),7.60 (1H,d,J=8.8Hz),7.67(1H,dd,J=1.6Hz,8.8Hz),7.81(1H,dd,J=1.6Hz,8.4Hz),7.95(1H,s), 8.02-8.06(2H,m),8.11(1H,d,J=8.8Hz),8.48(1H,s),8.98(2H,br),9.15(2H,s),9.46(2H,s)
16	NMR(DMSO-d_6) δ :1.77-1.87(2H,m),2.01(1.8H,s),2.24(1.2H,s),3.09(3H,s),3.44-3.76(8H,m), 4.98(2H,s),6.65-6.73(2H,m),7.16-7.23(2H,m),7.63-7.68(1H,m),7.78-7.84(1H,m),7.89-7.93 (1H,m),7.99-8.04(1H,m),8.09(1H,d,J=8.8Hz),8.49(0.4H,s),8.51(0.6H,s),8.61(0.6H,s),8.75 (0.4H,s),9.24-9.32(3H,m),9.51(2H,s)
17	NMR(DMSO-d_6) δ :1.78-1.87(5H,m),2.01(2H,s),2.25(1H,s),3.48-3.88(8H,m),4.99(2H,s),6.68-6.75(2H,m),6.95-7.03(2H,m),7.55-7.61(1H,m),7.79-7.87(2H,m),7.99-8.04(1H,m),8.11(1H,d, J=8.9Hz),8.49(0.3H,s),8.53(0.7H,s),8.64(0.7H,s), 8.78(0.3H,s),9.27-9.35(3H,m),9.50-9.56 (2H,s) MS(m/z):457(M-2HCl+1)$^+$

表１７

Ex	DATA
18	NMR(DMSO-d_6) δ :1.82-1.88(2H,m),2.03(2H,s),2.26(1H,s),3.45-3.71(8H,m),4.86(2H,s),6.72 (2H,br),7.13-7.20(3H,m),7.71(1H,d,J=8.6Hz),7.81-7.86(1H,m),7.91(1H,d,J=8.6Hz),8.00 (1H,d,J=8.6Hz),8.02(1H,d,J=8.6Hz),8.06-8.11(1H,m),8.74(1H,s),9.49(4H,br),9.63(2H,br)
19	NMR(DMSO-d_6) δ :1.28(3H,t,J=7.0Hz),1.78-1.85(2H,m),2.07(1.8H,s),2.33(1.2H,s),3.45-3.59 (5H,m),3.63-3.74(3H,m),4.15(2H,q,J=7.0Hz),5.12(1.2H,s),5.13(0.8H,s),6.69-6.74(2H,m), 7.06-7.10(2H,m),7.62-7.65(1H,m),7.81-7.84(1H,m),7.91(1H,s),8.02-8.05(1H,m),8.11 (1H,d,J=8.6Hz),8.49(0.4H,s),8.52(0.6H,s),8.67(0.6H,s),8.80(0.4H,s),9.31(2H,s),9.38(1H,s), 9.53(0.8H,s),9.54(1.2H,s),11.44(1H,s)
20	NMR(DMSO-d_6) δ :1.21(3H,t,J=7.0Hz),1.79-1.90(2H,m),2.09(2H,s),2.26(1H,s),3.40-3.80 (10H,m),4.11(2H,q,J=7.0Hz),4.94(2H,s),5.87(0.7H,t,J=5.9Hz),5.93(0.3H,t,J=5.9Hz), 6.70-6.77(2H,m),6.97-7.04(2H,m),7.59-7.64(1H,m),7.78-7.85(2H,m),7.99-8.04(1H,m),8.11 (1H,d,J=8.6Hz),8.44(0.7H,s),8.48(0.3H,s),8.62(0.7H,s),8.75(0.3H,s),9.22(2H,s),9.33(1H,s), 9.46-9.53(2H,m)
21	NMR(DMSO-d_6) δ :1.13(3H,t,J=7.0Hz),1.78-1.90(2H,m),2.07(2H,s),2.28(1H,s),3.48-3.83 (8H,m),4.01(2H,q,J=7.5Hz),4.95-5.01(2H,m),6.77(2H,d,J=8.6Hz),6.96-7.06(2H,m), 7.56-7.62(1H,m),7.82-7.91(2H,m),7.99-8.05(1H,m),8.11(1H,d,J=8.6Hz),8.49-8.64(2H,m), 8.79(0.7H,s),8.95(0.3H,s),9.44(2H,s),9.54(1H,s),9.59-9.66(2H,m)
22	NMR(DMSO-d_6) δ :1.25-1.29(3H,m),1.79-1.85(2H,m),2.03(2H,s), 2.25(1H,s),3.47-3.75(8H,m), 4.21-4.27(2H,m),4.37(2H,s), 5.00(2H,s),6.68-6.73(2H,m),7.17-7.21(2H,m),7.62-7.66(1H,m) , 7.82(1H,d,J=8.8Hz),7.90(1H,s),8.03(1H,dd,J=4.0Hz,8.8Hz),8.10(1H,d,J=8.8Hz),8.49 (0.4H,s),8.51(0.6H,s),8.64(0.6H,s),8.76(0.4H,s),9.29(2H,s),9.33(1H,s),9.53(2H,s) MS(m/z):565$(M-2HCl+1)^+$
23	NMR(DMSO-d_6) δ :1.22(3H,t,J=7.0Hz),1.80-1.86(2H,m),2.01(2H,s), 2.25(1H,s),3.49-3.54 (6H,m),3.66(2H,s),3.71-3.82(2H,m),4.13(2H,q,J=7.0Hz),4.90(2H,s), 6.66-6.75(2H,m),7.16-7.20(2H,m),7.62-7.67(1H,m),7.82-7.89(2H,m),8.08-8.11(2H,m),8.51(1H,s), 8.74(1H,s),9.43 (4H,br),9.62(2H,br) MS(m/z):580$(M-2HCl+1)^+$
24	NMR(DMSO-d_6) δ :1.13-1.18(3H,m),1.78-1.85(2H,m),2.03(2H,s),2.25(1H,s),3.26(1.4H,s),3.28 (0.6H,s),3.48-3.54(4H,m), 3.58-3.72(4H,m),4.00-4.07(2H,m),5.02(2H,s),6.69-6.73(2H,m), 6.69-7.01(2H,m),7.60-7.63(1H,m),7.80-7.83(1H,m),7.86(0.7H,s), 7.88(0.3H,s),8.04(1H,d, J=8.4Hz),8.12(1H,d,J=8.4Hz),8.45(0.3H,s),8.48(0.7H,s),8.60(0.7H,bs),8.74(0.3H,bs),9.24 (2H,br),9.28(1H,br),9.52(2H,s) MS(m/z):529$(M-2HCl+1)^+$
25	NMR(DMSO-d_6) δ :1.18(3H,t,J=7.0Hz),1.81-1.86(2H,m),2.01(2H,s),2.25(1H,s),2.29-2.36 (2H,m),2.52-2.57(2H,m),3.50-3.56(3H,m),3.58-3.62(1H,m),3.65-3.76(4H,m),4.06 (2H,q,J=7.0Hz),4.99(2H,s),6.71-6.76(2H,m),6.97-7.02(2H,m),7.56-7.58(1H,m),7.79-7.85 (2H,m),8.02(1H,d,J=8.6Hz),8.11(1H,d,J=8.6Hz),8.46(0.3H,s),8.49(0.7H,s),8.62(0.7H,s), 8.76(0.3H,s),9.27(2H,s),9.37(1H,s),9.52(2H,s)
26	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),1.86-1.97(2H,m),2.14-2.21(3H,brs),2.27(2H,s),2.34 (1H,s),2.97-3.03(2H,br),3.10-3.17(2H,m),3.66-3.75(4H,m),4.23(2H,q,J=7.0Hz),4.43 (2H,brs),5.07(2H,s),6.96-7.04(1H,m),7.19(1H,dd,J=2.1Hz,8.0Hz),7.27-7.30(1H,br),7.66 (1H,dd,J=1.4Hz,8.4Hz),7.85(1H,dd,J=1.4Hz,8.4Hz),7.93(1H,s),8.03(1H,d,J=8.6Hz), 8.09(1H,d,J=8.6Hz),8.53(1H,s),8.78(0.6H,s),8.85(0.4H,s),9.44(3H,s),9.61(2H,s)
27	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.0Hz),1.90-2.00(2H,m),2.25(2H,s),2.32(1H,s),3.09-3.18 (2H,m),3.20-3.40(2H,m),3.64-3.74(4H,m),4.22(2H,q,J=7.0Hz),4.51(2H,s),5.04(2H,s),7.12 (0.4H,d,J=8.8Hz),7.14(0.6H,d,J=8.8Hz),7.33(1H,dd,J=2.5Hz,8.8Hz),7.54(1H,d,J=2.5Hz), 7.64-7.68(1H,m),7.83(1H,dd,J=1.8Hz,8.4Hz),7.94(1H,s),8.03(1H,d,J=8.5Hz),8.10 (1H,d,J=8.5Hz),8.51(1H,s),8.74(0.6H,s),8.77(0.4H,s),9.37(3H,br),9.56(2H,br)

表１８

Ex	DATA
28	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.5Hz),1.78(2H,s),1.82(1H,s),1.83(2H,br),2.10(2H,s),2.29 (1H,s),3.50-3.61(5H,m),3.70(2H,br),3.79(1H,br),4.25(2H,q,J=7.5Hz),4.34(1H,d,J=14.0Hz), 4.54(1H,d,J=14.0Hz),5.13(2H,d,J=14.0Hz),6.54(1H,br),6.69(1H,br),7.37-7.40(1H,m), 7.58-7.63(1H,m),7.78(1H,s),7.86-7.92(1H,m),8.02-8.06(1H,m),8.09-8.14(1H,m),8.47(1H,s), 8.57(0.6H,s),8.79(0.4H,s),9.48(2H,s),9.56(1H,br),9.67(2H,s)
29	NMR(DMSO-d_6) δ :1.82(2H,br),2.11(2H,s),2.27(1H,s),3.51-3.59(8H,m),3.72(6H,s),4.43(2H,br) 4.91(1H,d,J=14.5Hz),5.13(1H,d,J=14.5Hz),6.86-6.92(1H,m),6.99(1H,br),7.14 (1H,d,J=9.1Hz),7.18(1H,d,J=9.1Hz),7.66-7.74(1H,m),7.87(1H,br),8.00-8.04(1H,m), 8.08-8.14(1H,m),8.54(1H,s),8.84(0.6H,s),8.98(0.4H,s),9.47(2H,s),9.55(1H,br),9.75(2H,br)
30	NMR(DMSO-d_6) δ :1.78-1.84(2H,m),2.03(2H,s),2.25(1H,s),3.28(1.3H,s),3.30(0.7H,s), 3.49-3.55(4H,m),3.57(1H,s),3.58(2H,s),3.60-3.75(4H,m),5.01(2H,s),6.70-6.73(2H,m), 6.96-7.00(2H,m),7.57-7.62(1H,m),7.81-7.91(2H,m),8.04(1H,d,J=8.6Hz),8.12(1H,d, J=8.6Hz),8.47(0.3H,s),8.51(0.7H,s),8.65(0.7H,s),8.80(0.3H,s),9.30(3H,br),9.55(2H,s)
31	NMR(DMSO-d_6) δ :1.82-1.89(2H,m),2.09(1.5H,s),2.28(1.5H,s),3.29-3.35(2H,m),3.39-3.42 (1H,m),3.47-3.50(1H,m), 3.60-3.70(3H,m),3.72-3.78(1H,m),4.33(2H,s),5.05(2H,s),6.86-6.92(1H,m),7.08-7.12(1H,m),7.25-7.29(1H,m),7.66(1H,dd,J=1.6Hz,8.6Hz),7.83(1H,d,J=8.6 Hz),7.93(1H,s),8.03(1H,d,J=8.6Hz),8.10(1H,d,J=8.6Hz),8.51(1H,s),8.73(1H,br),9.33(3H,br) ,9.53(2H,s)
32	NMR(DMSO-d_6) δ :1.79-1.83(2H,m),2.12(1.8H,s),2.25(1.2H,s),3.53-3.60(2H,m),3.64-3.70 (3H,m),3.73-3.82(2H,m), 3.84-3.88(1H,m),4.39(2H,s),5.04(2H,s),6.79-6.86(1H,m),7.64-7.69(2H,m),7.84(1H,dd,J=2.0Hz,10.2Hz),7.94(1H,s),8.01-8.06(2H,m),8.12(1H,d,J=11.3Hz) ,8.53(0.6H,s),8.54(0.4H,s),8.73(0.6H,s),8.82(0.4H,s),9.36(2H,s),9.41(0.4H,s),9.43(0.6H,s), 9.57(2H,s) MS(m/z):538(M-2HCl+1)$^+$
33	NMR(DMSO-d_6) δ :1.79-1.86(2H,m),2.03(2H,s),2.26(1H,s), 3.49-3.79(8H,m),4.26(2H,s),5.00 (1.4H,s),5.01(0.6H,s), 6.70-6.74(2H,m),7.18-7.22(2H,m),7.63-7.67(2H,m), 7.84-7.90(1H,m) ,8.02(0.3H,d,J=8.4Hz),8.03(0.7H,d,J=8.4Hz), 8.10(1H,d,J=8.4Hz),8.54(0.3H,s),8.57 (0.7H,s),8.75(0.7H,s), 8.92(0.3H,s),9.45(2H,s),9.48(1H,s),9.62(0.6H,s),9.63(1.4H,s) MS(m/z):537(M-2HCl+1)$^+$
34	NMR(DMSO-d_6) δ :1.80-1.87(2H,m),2.01(2H,s),2.25(1H,s), 3.46-3.56(4H,m),3.63-3.71(2H,m), 3.73(2H,s),3.75-3.79(2H,m),4.89(2H,s),6.76-6.84(2H,m), 7.13-7.20(2H,m),7.65(1H,dd,J= 3.8Hz,8.1Hz), 7.82-7.94(3H,m),8.01(1H,d,J=8.1Hz),8.08(1H,d,J=8.6Hz), 8.65(1H,s),9.42 (4H,br),9.61(2H,br)
35	NMR(DMSO-d_6) δ :1.78-1.86(2H,m),2.03(2H,s),2.25(1H,s), 3.17(1.4H,s),3.19(0.6H,s), 3.49-3.55(4H,m),3.59-3.74(4H,m),5.02(2H,s),6.70-6.74(2H,m),6.97-7.02(2H,m),7.60-7.62 (1H,m),7.78-7.83(1H,m),7.90(0.7H,s),7.92(0.3H,s),8.03(1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz) ,8.45(0.7H,s),8.48(0.7H,s),8.61(0.7H,s),8.75(0.3H,s),9.27(3H,br),9.53(2H,s)
36	NMR(DMSO-d_6) δ :1.80-1.82(2H,m),2.04(2H,s),2.25(1H,s),2.26-2.33(2H,m),2.46-2.52(2H,m), 3.48-3.75(8H,m),4.99(2H,s),6.71-6.74(2H,m),6.99-7.06(2H,m),7.56-7.59(1H,m),7.95-7.82 (1H,m),7.86(1H,br),8.00(1H,d,J=9.2Hz), 8.12(1H,d,J=9.2Hz),8.44(0.3H,s),8.45(0.7H,s), 8.53(0.7H,br),8.65(0.3H,br),9.17(3H,br),9.47(2H,s), MS(m/z):515(M-2HCl+1)$^+$
37	NMR(DMSO-d_6) δ :1.78-1.92(2H,m),2.08(2H,s),2.33(1H,s),3.47-3.82(10H,m),4.94(2H,s), 5.70-5.90(1H,m),6.78(2H,d,J=7.5Hz),6.98-7.07(2H,m),7.62(1H,d,J=8.5Hz),7.80-7.87 (2H,m),7.98-8.04(1H,m),8.10(1H,d,J=8.9Hz),8.47(0.3H,s), 8.52(0.7H,s),8.73(0.7H,s),8.90 (0.3H,s),9.39(2H,s),9.49(1H,s),9.54-9.62(2H,m)
38	NMR(DMSO-d_6) δ :1.86-1.96(2H,m),2.18(3H,br),2.26(2H,s),2.33(1H,s),2.98(2H,br),3.12 (2H,br),3.66-3.71(4H,m),4.29(2H,br),5.06(2H,s),6.98-7.02(1H,m),7.19(1H,d,J=6.0Hz),7.29 (1H,br),7.66(1H,d,J=8.8Hz),7.82(1H,dd,J=1.6Hz,8.8Hz),7.94(1H,s),8.02(1H,d,J=8.8Hz), 8.09(1H,d,J=8.8Hz),8.51(1H,s),8.70(0.6H,s),8.76(0.4H,s),9.35(3H,s),9.54(2H,s)

表19

Ex	DATA
39	NMR(DMSO-d_6) δ :1.82(2H,br),2.11(2H,s),2.27(1H,s),3.51-3.59(8H,m),3.72(6H,s),4.43 (2H,br),4.91(1H,d,J=14.5Hz),5.13(1H,d,J=14.5Hz),6.86-6.92(1H,m),6.99(1H,br),7.14 (1H,d,J=9.1Hz),7.18(1H,d,J=9.1Hz),7.66-7.74(1H,m),7.87(1H,br),8.00-8.04(1H,m), 8.08-8.14(1H,m),8.54(1H,s),8.84(0.6H,s),8.98(0.4H,s),9.47(2H,s),9.55(1H,br),9.75(2H,br)
40	NMR(DMSO-d_6) δ :1.99-2.06(2H,m),3.03-3.08(2H,m),3.12-3.16(2H,m),3.41(2H,t,J=6.0Hz), 3.61-3.65(2H,m),4.23(2H,s),5.01(2H,s),6.68(2H,d,J=9.1Hz),7.21(2H,d,J=9.1Hz),7.66 (1H,dd,J=1.6Hz,8.6Hz),7.79-7.82(1H,m),7.91(1H,s),8.02(1H,d,J=8.6Hz),8.10 (1H,d,J=8.6Hz),8.47(1H,s),9.12(2H,br),9.23(2H,br),9.48(2H,s)
41	NMR(DMSO-d_6) δ :2.01-2.07(2H,m),3.03-3.08(2H,m),3.12-3.16(2H,m),3.20(2H,s),3.43 (2H,t,J=5.9Hz),3.63-3.67(2H,m),5.03(2H,s),6.70(2H,d,J=9.2Hz),7.02(2H,d,J=9.2Hz),7.63 (1H,dd,J=1.6Hz,8.6Hz),7.81(1H,dd,J=1.6Hz,8.6Hz),7.91(1H,s),8.02(1H,d,J=8.6Hz),8.12 (1H,d,J=8.6Hz),8.44(1H,s),9.16(2H,br),9.23(2H,s),9.50(2H,s)
42	NMR(DMSO-d_6) δ :2.00-2.06(2H,m),2.32(2H,t,J=6.4Hz),2.51(2H,t,J=6.4Hz),3.06-3.11(2H,m), 3.15-3.19(2H,m),3.40-3.46(2H,m),3.61-3.66(2H,m),5.00(2H,s),6.71(2H,d,J=8.8Hz),7.03 (2H,d,J=8.8Hz),7.58(1H,dd,J=1.6Hz,8.6Hz),7.78(1H,dd,J=1.6Hz,8.6Hz),7.86(1H,s),8.00 (1H,d,J=8.6Hz),8.11(1H,d,J=8.6Hz),8.43(1H,s),8.93(2H,br),9.12(2H,s),9.45(2H,s)
43	NMR(DMSO-d_6) δ :1.26(1H,t,J=7.0Hz),1.83-1.89(2H,m),2.09(1.5H,s),2.29(1.5H,s),3.30-3.36 (2H,m),3.40-3.43(1H,m),3.47-3.51(1H,m),3.61-3.70(3H,m),3.76-3.80(1H,m),4.23 (2H,q,J=7.0Hz),4.47(2H,s),5.06(2H,s),6.87-6.93(1H,m),7.07-7.11(1H,m),7.25-7.29(1H,m), 7.65(1H,d,J=8.6Hz),7.84(1H,d,J=8.6Hz),7.93(1H,s),8.07(1H,d,J=8.0Hz),8.10(1H,d, J=8.0Hz),8.52(0.5H,s),8.54(0.5H,s),8.80(0.5H,s),8.82(0.5H,s),9.41-9.46(3H,m),9.59(2H,br)
44	NMR(DMSO-d_6) δ :1.24-1.28(3H,m),1.78-1.85(2H,m),2.12(18H,s),2.25(1.2H,s),3.53-3.61 (2H,m),3.64-3.70(3H,m),3.74-3.81(2H,m),3.84-3.88(1H,m),4.22-4.27(2H,m),4.52(2H,s), 5.04(2H,s),6.78-6.86(1H,m),7.64-7.68(2H,m),7.84(1H,d,J=8.6Hz),7.93(1H,s),8.02-8.06 (2H,m),8.12(1H,d,J=8.6Hz),8.53(0.6H,s),8.55(0.4H,s),8.75(0.6H,br),8.84(0.4H,br), 9.34-9.46(3H,m),9.58(2H,br)
45	NMR(DMSO-d_6) δ :2.01-2.07(2H,m),3.02-3.07(4H,m),3.11-3.16(2H,m),3.41-3.45(2H,m),3.64-3.67(2H,m),5.03(2H,s),6.69(2H,t,J=9.3Hz),6.95(1H,s),7.04(2H,d,J=9.3Hz),7.39(1H,s),7.64 (1H,dd,J=1.2Hz,8.8Hz),7.80(1H,dd,J=1.2Hz,8.4Hz),7.94(1H,s),8.02(1H,d,J=8.4Hz),8.14 (1H,d,J=8.8Hz),8.43(1H,s),9.17(2H,s),9.23(2H,s),9.51(2H,s)
46	NMR(DMSO-d_6) δ :0.99(3H,t,J=3.0Hz),2.01-2.07(2H,m),3.01-3.08(6H,m),3.41-3.44(2H,m), 3.63-3.67(2H,m),5.02(2H,s),6.68(2H,d,J=9.0Hz),7.02(2H,d,J=9.0Hz),7.64(1H,dd,J=1.6Hz, 8.0Hz),7.80(1H,dd,J=1.6Hz,8.8Hz),7.88-7.91(2H,m),8.02(1H,d,J=8.8Hz),8.13 (1H,d,J=8.0Hz),8.43(1H,s),9.14-9.24(4H,m),9.50(2H,s)
47	NMR(DMSO-d_6) δ :0.83(3H,t,J=6.8Hz),0.98(3H,t,J=6.8Hz),1.93-2.00(2H,m),2.88-2.92(2H,m), 3.00-3.10(4H,m),3.18-3.42(6H,m),3.56-3.60(2H,m),5.02(2H,s),6.34(2H,d,J=8.8Hz), 6.99(2H,d,J=8.8Hz),7.70(1H,dd,J=1.4Hz,8.3Hz),7.80(1H,dd,J=2.0Hz,8.8Hz),7.91(1H,s), 8.03(1H,d,J=8.3Hz),8.12(1H,d,J=8.8Hz),8.41(1H,s)
48	NMR(DMSO-d_6) δ :1.15(3H,t,J=6.8Hz),2.01-2.11(2H,m),3.02-3.20(4H,m),3.39-3.45(2H,m), 3.62-3.67(2H,m),4.11(2H,q,J=6.8Hz),4.99(2H,s),6.66(2H,d,J=8.7Hz),7.02(2H,d,J=8.7Hz), 7.60(1H,d,J=8.8Hz),7.82(1H,d,J=8.8Hz),7.86(1H,s),8.03(1H,d,J=8.3Hz),8.11(1H,d, J=8.3Hz),8.50(1H,s),9.22-9.37(4H,m),9.49-9.56(2H,s)
49	NMR(DMSO-d_6) δ :1.22(3H,t,J=7.3Hz),2.03-2.11(2H,m),3.00-3.15(4H,m),3.40-3.46(2H,m), 3.64-3.70(2H,m),4.11(2H,q,J=7.3Hz),4.22(2H,d,J=5.8Hz),5.62(2H,s),6.75(2H,d,J=9.3Hz), 6.98(2H,d,J=9.3Hz),7.14(1H,t,J=5.8Hz),7.71(1H,dd,J=1.4Hz,8.8Hz),7.81(1H,dd,J=1.4Hz, 8.8Hz),7.89(1H,s),8.01(1H,d,J=8.8Hz),8.11(1H,d,J=8.8Hz),8.45(1H,s),9.22-9.35(4H,m), 9.51(2H,s)

表２０

Ex	DATA
50	NMR(DMSO-d_6) δ :2.02-2.10(2H,m),3.03-3.09(2H,m),3.11-3.18(2H,m),3.42-3.48(2H,m),3.64-3.71(2H,m),3.91(2H,s),5.06(2H,s),6.73(2H,d,J=8.8Hz),7.11(2H,d,J=8.8Hz),7.63(1H,dd,J=1.4Hz,8.3Hz),7.81(1H,dd,J=1.4Hz,8.3Hz),7.91(1H,s),8.03(1H,d,J=8.3Hz),8.12(1H,d,J=8.3Hz),8.49(1H,s),9.29(4H,br),9.53(2H,s)
51	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),2.04-2.16(1H,m),2.28-2.40(1H,m),2.71(1.5H,s),2.72(1.5H,s),2.99-3.09(2H,m),3.26-3.42(4H,m),3.62-3.76(2H,m),4.25(2H,q,J=7.2Hz),4.36(2H,s),5.02(2H,s),6.67(2H,d,J=8.4Hz),7.22(2H,d,J=8.4Hz),7.67(1H,d,J=8.4Hz),7.83(1H,d,J=8.4Hz),7.90(1H,s),8.03(1H,d,J=8.4Hz),8.10(1H,d,J=8.4Hz),8.51(1H,s),9.37(2H,s),9.56(2H,s),11.21(1H,s)
52	NMR(DMSO-d_6) δ :2.08-2.12(1H,m),2.29-2.41(1H,m),2.70(1.5H,s),2.72(1.5H,s),2.96-3.08(5H,m),3.25-3.42(4H,m),3.62-3.76(2H,m),5.00(2H,s),6.65(2H,d,J=8.8Hz),7.23(2H,d,J=8.8Hz),7.68(1H,dd,J=1.6Hz,8.4Hz),7.84(1H,d,J=8.0Hz),7.90(1H,s),8.01(1H,d,J=8.4Hz),8.09(1H,d,J=8.0Hz),8.54(1H,s),9.44(2H,s),9.61(2H,s),11.30(1H,s)
53	NMR(DMSO-d_6) δ :1.29(3H,t,J=7.2Hz),2.04-2.14(1H,m),2.29-2.40(1H,m),2.71(1.5H,s),2.73(1.5H,s),2.99-3.09(2H,m),3.28-3.40(4H,m),3.61-3.72(2H,m),4.24(2H,q,J=7.2Hz),5.14(2H,s),6.68(2H,d,J=8.8Hz),7.11(2H,d,J=8.8Hz),7.68(1H,dd,J=1.6Hz,8.8Hz),7.83(1H,dd,J=1.6Hz,8.4Hz),7.91(1H,s),8.03(1H,d,J=8.4Hz),8.10(1H,d,J=8.4Hz),8.49(1H,s),9.35(2H,s),9.55(2H,s),11.22(1H,s),11.41(1H,s)
54	NMR(DMSO-d_6) δ :2.04-2.12(1H,m),2.25-2.37(1H,m),2.71(1.5H,s),2.72(1.5H,s),2.97-3.07(2H,m),3.25-3.42(4H,m),3.60-3.72(2H,m),4.87(2H,s),5.30-5.85(2H,br),6.62(2H,d,J=8.8Hz),7.17(2H,d,J=8.8Hz),7.73(1H,dd,J=1.6Hz,8.8Hz),7.81(1H,dd,J=1.6Hz,8.8Hz),7.72(1H,s),7.99(1H,d,J=8.8Hz),8.08(1H,d,J=8.8Hz),8.45(1H,s),9.34(2H,s),9.54(2H,s),11.16(1H,s)
55	NMR(DMSO-d_6) δ :2.03-2.15(1H,m),2.28-2.38(1H,m),2.67(3H,s),2.71(3H,d,J=4.9Hz),2.97-3.11(2H,m),3.22-3.46(4H,m),3.60-3.75(2H,m),4.93(2H,s),6.62(2H,d,J=9.2Hz),7.17(2H,d,J=9.2Hz),7.67(1H,br d),7.82(1H,dd,J=1.8Hz,8.6Hz),7.90(1H,br s),8.00(1H,d,J=8.6Hz),8.08(1H,d,J=8.6Hz),8.48(1H,s),9.35(2H,s),9.55(2H,s),11.16(1H,br s)
56	NMR(DMSO-d_6) δ :2.02-2.16(1H,m),2.25-2.40(1H,m),2.71(3H,d,J=4.4Hz),2.78(6H,s),2.98-3.10(2H,m),3.24-3.48(4H,m),3.60-3.80(2H,m),5.00(2H,s),6.63(2H,d,J=8.8Hz),7.21(2H,d,J=8.8Hz),7.66(1H,dd,J=1.6Hz,8.4Hz),7.82(1H,dd,J=1.6Hz,8.4Hz),7.88(1H,br s),8.01(1H,d,J=8.4Hz),8.09(1H,d,J=8.4Hz),8.49(1H,s),9.34(2H,s),9.55(2H,s)
57	NMR(DMSO-d_6) δ :0.85-0.89(3H,m),1.23-1.30(5H,m),1.59-1.72(2H,m),2.06-2.13(1H,m),2.31-2.41(1H,m),2.95-3.05(4H,m),3.25-3.45(4H,m),3.68-3.73(2H,m),4.25(2H,q,J=7.2Hz),4.36(2H,s),5.02(2H,s),6.66(2H,d,J=8.8Hz),7.22(2H,d,J=8.8Hz),7.66(1H,dd,J=1.6Hz,8.8Hz),7.82(1H,dd,J=1.6Hz,8.8Hz),7.91(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.48(1H,s),9.28(2H,s),9.51(2H,s),10.88(1H,s)
58	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.6Hz),2.07-2.16(1H,m),2.39-2.49(1H,m),2.91-3.02(2H,m),3.24-3.42(4H,m),3.72-3.76(2H,m),4.22-4.34(4H,m),4.35(2H,s),5.02(2H,s),6.66(2H,d,J=8.8Hz),7.20(2H,d,J=8.8Hz),7.41-7.44(3H,m),7.61-7.68(3H,m),7.83(1H,dd,J=1.2Hz,8.8Hz),7.90(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.50(1H,s),9.34(2H,s),9.54(2H,s),11.41(1H,s)
59	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.78-1.83(2H,m),3.36-3.38(2H,m),3.44-3.49(2H,m),3.52-3.58(4H,m),4.24(2H,q,J=7.2Hz),4.38(2H,s),5.00(2H,s),6.69(2H,d,J=9.2Hz),7.18(2H,d,J=9.2Hz),7.37(4H,s),7.64(1H,dd,J=1.2Hz,8.4Hz),7.81(1H,dd,J=1.4Hz,8.8Hz),7.91(1H,s),8.03(1H,d,J=8.8Hz),8.11(1H,d,J=8.4Hz),8.47(1H,s),9.20(2H,s),9.47(2H,s)
60	NMR(DMSO-d_6) δ :1.15(3H,t,J=7.1Hz),1.73-1.83(2H,m),2.53-2.68(2H,m),2.68-2.86(2H,m),3.08(3H,s),3.29-3.41(6H,m),4.03(2H,br s),4.97(2H,s),6.58(2H,d,J=8.8Hz),7.16(2H,d,J=8.8Hz),7.66(1H,dd,J=1.5Hz,8.8Hz),7.79(1H,dd,J=1.5Hz,8.8Hz),7.92(1H,s),8.01(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.45(1H,s),9.18(2H,s),9.45(2H,s)

表２１

Ex	DATA
61	NMR(DMSO-d_6) δ :1.79-1.85(2H,m),2.49-2.53(2H,m),2.65-2.69(2H,m),2.94(2H,s),3.08(3H,s), 3.36-3.39(2H,m),3.42-3.45(2H,m),4.96(2H,s),6.58(2H,d,J=9.0Hz),7.03(1H,s),7.13(1H,s), 7.15(2H,d,J=9.0Hz),7.64(1H,dd,J=1.5Hz,8.3Hz),7.79(1H,dd,J=1.5Hz,8.8Hz),7.88(1H,s), 7.99(1H,s),8.05(1H,s),8.39(1H,s),9.90(2H,br)
62	NMR(DMSO-d_6) δ :1.16(3H,t,J=7.4Hz),2.05-2.12(2H,m),3.08-3.24(4H,m),3.37(2H,s),3.63-3.68 (2H,m),3.92-3.96(2H,m),4.05(2H,q,J=7.4Hz),5.06(2H,s),6.91(1H,d,J=9.2Hz),7.57(1H,d,J= 9.2Hz),7.63(1H,dd,J=1.5Hz,8.8Hz),7.84(1H,dd,J=1.2Hz,8.8Hz),7.89(1H,s),7.91(1H,d,J=2.5 Hz),8.05(1H,d,J=8.8Hz),8.13(1H,d,J=8.8Hz),8.50(1H,s),9.37(2H,s),9.53(2H,s),9.58(2H,s)
63	NMR(DMSO-d_6) δ :1.19(3H,t,J=1.2Hz),2.04-2.11(2H,m),2.39(2H,t,J=6.4Hz),2.58(2H,t,J=6.4 Hz),3.10-3.20(4H,m),3.64-3.68(2H,m),3.91-3.95(2H,m),4.07(2H,q,J=7.2Hz),5.03(2H,s), (1H,d,J=8.0Hz),7.55-7.61(2H,m),7.83(1H,d,J=8.8Hz),7.87(1H,s),7.95(1H,d,J=2.8Hz),8.03 (1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz),8.49(1H,s),9.35(2H,s),9.45(2H,s),9.56(2H,s)
64	NMR(DMSO-d_6) δ :0.87(3H,t,J=7.2Hz),1.24-1.32(2H,m),1.48-1.54(2H,m),1.78-1.85(2H,m), 2.03(2H,s),2.26(1H,s),3.26(1.3H,s),3.28(0.7H,s),3.52-3.78(8H,m),3.99(2H,t,J=6.8Hz),5.02 (2H,s),6.70-6.73(2H,m),6.95-7.00(2H,m),7.60-7.64(1H,m),7.83-7.87(2H,m),8.02-8.06 (1H,m),8.13(1H,d,J=8.8Hz),8.49(0.3H,s),8.55(0.7H,s),8.73(0.7H,s),8.89(0.3H,s),9.41(2H,s) ,9.45(1H,s).9.60-9.62(2H,m)
65	NMR(DMSO-d_6) δ :1.14-1.17(6H,m),1.78-1.84(2H,m),2.03(1.8H,s),2.26(1.2H,s),3.22(1.3H,s), 3.24(0.7H,s),3.50-3.78(8H,m),4.82-4.89(1H,m),5.02(2H,s),6.69-6.75(2H,m),6.94-7.00 (2H,m),7.63(1H,d,J=8.8Hz),7.83-7.87(2H,m),8.03-8.06(1H,m),8.12(1H,d,J=8.8Hz),8.50 (0.4H,s),8.56(0.6H,s),8.75(0.6H,s),8.92(0.4H,s),9.43-9.48(3H,m),9.61-9.64(2H,m)
66	NMR(DMSO-d_6) δ :1.78-1.85(2H,m),2.04(2H,s),2.25(1H,s),3.04-3.07(2H,m),3.49-3.75(8H,m), 5.02(2H,s),6.69-6.73(2H,m),6.83(1H,s),6.99-7.04(2H,m),7.41(1H,s),7.61-7.65(1H,m),7.80-7.84(1H,m),7.92(0.7H,s),7.94(0.3H,s),8.01(1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz),8.46(0.3H,s),8.50(0.7H,s),8.67(0.7H,s),8.81(0.3H,s),9.34(2H,s),9.38-9.41(1H,m),9.55-9.57(2H,m)
67	NMR(DMSO-d_6) δ :0.96-1.00(3H,m),1.78-1.86(2H,m),2.04(2H,s),2.25(1H,s),3.00-3.07(4H,m), 3.43-3.56(4H,m),3.57-3.74(4H,m),5.01(2H,s),6.68-6.72(2H,m),6.98-7.03(2H,m),7.61-7.65 (1H,m),7.79-7.82(1H,m),7.88-7.92(2H,m),8.03(1H,d,J=8.8Hz),8.12(1H,d,J=8.7Hz),8.44 (0.3H,s),8.47(0.7H,s),8.61(0.7H,s),8.74(0.3H,s),9.25(2H,s),9.30-9.33(1H,m),9.53(2H,s)
68	NMR(DMSO-d_6) δ :0.78(1.2H,t,J=7.2Hz),0.84(1.8H,t,J=7.2Hz),0.95-1.00(3H,m),1.74-1.85 (2H,m),2.07(1.8H,s),2.25(1.2H,s),3.00-3.10(2H,m),3.17-3.27(4H,m),3.44-3.54(4H,m),3.56-3.74(4H,m),5.01(2H,s),6.65-6.71(2H,m),6.96-7.00(2H,m),7.67-7.72(1H,m),7.80-7.84(1H,m) ,7.89(0.6H,s),7.92(0.4H,s),8.02(0.6H,s),8.05(0.4H,s),8.11(0.6H,s),8.13(0.4H,s),8.43(0.4H,s),8.48(0.6H,s),8.66(0.6H,s),8.80(0.4H,s),9.29(2H,s),9.37-9.39(1H,m),9.53-9.55(2H,m)
69	NMR(DMSO-d_6) δ :1.15(3H,m),1.79-1.88(2H,m),2.03(2H,s),2.26(1H,s),3.48-3.61(4H,m), 3.65-3.78(4H,m),4.10(2H,q,J=6.9Hz),4.98(2H,s),6.65-6.72(2H,m),6.96-7.06(2H,m),7.59 (1H,d,J=8.8Hz),7.82(1H,dd,J=1.9Hz,8.8Hz),7.85(1H,s),8.03(1H,d,J=8.8Hz),8.11(1H,d, J=8.8Hz),8.52(1H,d,J=8.8Hz),8.63(0.7H,s),8.77(0.3H,s),9.30(3H,s),9.53(3H,s)
70	NMR(DMSO-d_6) δ :1.22(3H,t,J=7.3Hz),1.77-1.87(2H,m),2.06(0.7H,s),2.27(0.3H,s),3.46-3.79 (8H,m),4.11(2H,q,J=7.3Hz),4.23(2H,d,J=5.9Hz),5.60(2H,s),6.73-6.81(2H,m),6.93-7.00 (2H,m),7.09(0.7H,t,J=5.8Hz),7.15(0.3H,t,J=5.8Hz),7.70(1H,d,J=8.3Hz),7.80-7.85(1H,m), 7.83(1H,s),7.99-8.40(1H,m),8.11(1H,d,J=8.8Hz),8.47(0.3H,s),8.53(0.7H,s),8.70(0.7H,s), 8.80(0.3H,s),9.32(2H,s),9.41-9.46(1H,m),9.51-9.80(2H,m)
71	NMR(DMSO-d_6) δ :1.79-1.88(2H,m),2.05(2H,s),2.26(1H,s),3.49-3.79(8H,m),3.89(1.3H,s),3.91 (0.7H,s),5.05(2H,s),6.71-6.78(2H,m),7.05-7.12(2H,m),7.59-7.64(1H,m),7.80-7.85(1H,m), 7.91(1H,d,J=8.8Hz),8.03(1H,dd,J=1.4Hz,8.8Hz),8.12(1H,d,J=8.8Hz),8.51(0.3H,s),8.55 (0.7H,s),8.66(0.7H,s),8.81(0.3H,s),9.29-9.37(3H,m),9.53-9.58(2H,m)

表２２

Ex	DATA
72	NMR(DMSO-d_6) δ :1.14-1.18(3H,m),1.78-1.86(2H,m),2.14(1.8H,s),2.27(1.2H,s),3.35(1.2H,s),3.37(0.8H,s),3.56-3.61(2H,m),3.66-3.94(6H,m),4.01-4.07(2H,m),5.05(2H,s),6.89-6.95(1H,m),7.50-7.53(1H,m),7.63(1H,d,J=8.4Hz),7.84-7.93(3H,m),8.04-8.08(1H,m),8.13(1H,d,J=8.4Hz),8.52(0.4H,s),8.56(0.6H,s),8.84(0.6H,s),8.93(0.4H,s),9.44(2H,s),9.53-9.56(1H,m),9.64(2H,s)
73	NMR(DMSO-d_6) δ :1.19(3H,t,J=6.8Hz),1.80-1.87(2H,m),2.13(1.8H,s),2.27(1.2H,s),2.33-2.41(2H,m),2.55-2.61(2H,m),3.58-3.62(2H,m),3.68-3.95(6H,m),4.07(2H,q,J=6.8Hz),5.24(2H,s),6.91-6.97(1H,m),7.51-7.61(2H,m),7.83-7.88(2H,m),7.93(1H,dd,J=2.4Hz,12.8Hz),8.04(1H,dd,J=3.2Hz,8.8Hz),8.12(1H,d,J=8.8Hz),8.52(0.4H,s),8.55(0.6H,s),8.81(0.6H,s),8.90(0.4H,s),9.42(2H,s),9.52(0.4H,s),9.56(0.6H,s),9.62(2H,s)
74	NMR(DMSO-d_6) δ :2.02-2.09(2H,m),3.01-3.09(2H,m),3.09-3.16(2H,m),3.40-3.45(2H,m),3.63-3.69(2H,m),4.18(2H,q,J=5.4Hz),5.62(2H,s),6.75(2H,d,J=8.7Hz),6.97-7.03(2H,m),7.69(1H,d,J=8.7Hz),7.80(1H,d,J=8.7Hz),7.92(1H,s),8.01(1H,d,J=8.7Hz),8.10(1H,d,J=8.7Hz),8.44(1H,s),9.11-9.19(4H,m),9.47(2H,s),12.53(1H,br)
75	NMR(DMSO-d_6) δ :1.78-1.88(2H,m),2.07(0.7H,s),2.26(0.3H,s),3.45-3.76(8H,s),4.18(2H,d,J=5.4Hz),5.60(2H,s),6.74-6.81(2H,m),6.94(1H,t,J=5.4Hz),6.95-7.02(2H,m),7.68(1H,d,J=8.3Hz),7.79-7.83(1H,m),7.92(1H,s),7.99-8.03(1H,m),8.11(1H,d,J=8.3Hz),8.45(0.3H,s),8.50(0.7H,s),8.64(0.7H,s),8.76(0.3H,s),9.24(2H,s),9.34(1H,s),9.48-9.54(2H,m),12.56(1H,br)
76	NMR(DMSO-d_6) δ :2.73(3H,s),3.01-3.11(2H,m),3.31-3.33(6H,m),3.52-3.55(2H,m),4.23(2H,s),5.02(2H,s),6.66(2H,d,J=8.8Hz),7.22(2H,d,J=8.8Hz),7.67(1H,d,J=8.8Hz),7.80(1H,dd,J=2.0Hz,8.8Hz),7.92(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.47(1H,s),9.20(2H,s),9.47(2H,s),10.73(1H,s)
77	NMR(DMSO-d_6) δ :0.87(3H,t,J=7.4Hz),1.22-1.31(2H,m),1.59-1.71(2H,m),2.06-2.14(1H,m),2.32-2.43(1H,m),2.95-3.05(4H,m),3.25-3.47(4H,m),3.69-3.74(2H,m),4.24(2H,s),5.02(2H,s),6.66(2H,d,J=9.2Hz),7.22(2H,d,J=9.2Hz),7.67(1H,dd,J=1.2Hz,8.8Hz),7.82(1H,dd,J=1.2Hz,8.8Hz),7.91(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.49(1H,s),9.32(2H,s),9.53(2H,s),10.96(1H,s)
78	NMR(DMSO-d_6) δ :2.08-2.16(1H,m),2.38-2.49(1H,m),2.92-3.02(2H,m),3.24-3.46(4H,m),3.72-3.77(2H,m),4.23(2H,s),4.25-4.35(2H,m),5.02(2H,s),6.65(2H,d,J=8.8Hz),7.21(2H,d,J=8.8Hz),7.41-7.44(3H,m),7.60-7.64(2H,m),7.67(1H,dd,J=1.5Hz,8.8Hz),7.82(1H,dd,J=1.2Hz,8.8Hz),7.90(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.49(1H,s),9.32(2H,s),9.53(2H,s),11.35(1H,s)
79	NMR(DMSO-d_6) δ :1.79-1.84(1H,m),3.35-3.39(2H,m),3.45-3.49(2H,m),3.52-3.55(2H,m),3.58-3.62(2H,m),4.26(2H,s),5.00(2H,s),6.70(2H,d,J=8.8Hz),7.19(2H,d,J=8.8Hz),7.51(4H,s),7.65(1H,dd,J=1.0Hz,8.8Hz),7.83(1H,dd,J=0.9Hz,8.8Hz),7.91(1H,s),8.03(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.51(1H,s),9.38(2H,s),9.56(2H,s)
80	NMR(DMSO-d_6) δ :1.98-2.05(2H,m),3.06-3.17(4H,m),3.54-3.58(2H,m),3.81-3.85(2H,m),4.33(2H,s),5.03(2H,s),6.68(1H,d,J=9.2Hz),7.59(1H,dd,J=2.8Hz,9.2Hz),7.66-7.69(1H,m),7.79-7.82(1H,m),7.95(1H,s),8.02-8.05(2H,m),8.11(1H,d,J=8.4Hz),8.49(1H,s),9.09(2H,s),9.21(2H,s),9.48(2H,s)
81	NMR(DMSO-d_6) δ :2.06-2.12(2H,m),3.12-3.22(4H,m),3.31(2H,s),3.66-3.70(2H,m),3.95-3.98(2H,m),5.06(2H,s),7.01(1H,d,J=9.2Hz),7.62-7.66(2H,m),7.84(1H,dd,J=1.2Hz,8.4Hz),7.93-7.95(2H,m),8.05(1H,d,J=8.0Hz),8.13(1H,d,J=8.8Hz),8.50(1H,s),9.40(2H,s),9.60(4H,s)
82	NMR(DMSO-d_6) δ :1.79-1.86(2H,m),2.13(1.8H,s),2.27(1.2H,s),3.27(1.2H,s),3.28(0.8H,s),3.56-3.62(2H,m),3.68-3.92(6H,m),5.04(2H,s),6.88-6.94(1H,m),7.49-7.56(1H,m),7.63(1H,d,J=8.4Hz),7.83-7.86(1H,m),7.90-7.94(2H,m),8.03-8.06(1H,m),8.13(1H,d,J=8.8Hz),8.50(0.4H,s),8.54(0.6H,s),8.79(0.6H,s),8.88(0.4H,s),9.40(2H,s),9.48(1H,s),9.61(2H,s)

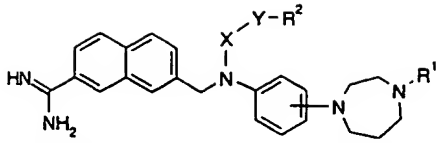
表２３

Ex	DATA
83	NMR(DMSO-d_6) δ :2.06-2.12(2H,m),2.36(2H,t,J=6.4Hz),2.52(2H,t,J=6.4Hz),3.12-3.22(4H,m), 3.65-3.69(2H,m),3.93-3.97(2H,m),5.26(2H,s),6.97-7.02(1H,m),7.59-7.67(2H,m),7.83 (1H,dd,J=2.0Hz,8.8Hz),7.89(1H,s),7.96(1H,d,J=2.4Hz),8.02(1H,d,J=8.8Hz), 8.12(1H,d,J=8.8Hz),8.50(1H,s),9.38(2H,s),9.51(2H,s),9.58(2H,s)
84	NMR(DMSO-d_6) δ :1.81-1.87(2H,m),2.14(2H,s),2.28(1H,s),2.31-2.37(2H,m),2.51-2.55(2H,m), 3.59-3.63(2H,m),3.70-3.96(6H,m),5.03(2H,s),6.94-7.00(1H,m),7.55-7.61(2H,m),7.83-7.90 (2H,m),7.00(1H,dd,J=2.4Hz,12.0Hz),8.03(1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz),8.52(0.3H,s), 8.55(0.7H,s),8.82(0.7H,s),8.91(0.3H,s),9.44(2H,s),9.53(0.3H,s),9.57(0.7H,s),9.63(2H,s)
85	NMR(DMSO-d_6) δ :1.86-1.94(2H,m),2.81-2.84(2H,m),2.93-2.97(2H,m),3.09(3H,s),3.34-3.37 (4H,m),3.48-3.51(2H,m),4.97(2H,s),6.60(2H,d,J=9.0Hz),7.17(2H,d,J=9.0Hz),7.67 (1H,d,J=8.8Hz),7.79(1H,d,J=8.8Hz),7.91(1H,s),8.01(1H,d,J=8.8Hz),8.09(1H,d,J=8.8Hz), 8.46(1H,s),9.27(2H,s),9.46(2H,s)
86	NMR(DMSO-d_6) δ :0.96(6H,s),2.86-2.89(2H,m),3.09(3H,s),3.28-3.33(2H,m),3.35(2H,s),3.35 (2H,t,J=5.4Hz),4.99(2H,s),6.74(2H,d,J=8.8Hz),7.19(2H,d,J=8.8Hz),7.67(1H,dd,J=1.4Hz, 8.8Hz),7.83(1H,dd,J=1.9Hz,8.8Hz),7.91(1H,s),8.01(1H,d,J=8.8Hz),8.09(1H,d,J=8.8Hz); 8.51(1H,s),9.37(4H,s),9.56(2H,s)
87	NMR(DMSO-d_6) δ :0.89(3H,s),0.92(3H,s)2.25(1.5H,s),2.29(1.5H,s),3.09(3H,s),3.30(1H,s), 3.34(1H,s),3.43-3.54(4H,m),3.81-3.86(2H,m),4.99(2H,s),6.68(1H,d,J=9.2Hz),6.72 (1H,d,J=9.2Hz),7.16-7.21(2H,m),7.65-7.68(1H,m),7.84(1H,dd,J=1.6Hz,8.4Hz),7.90(1H,s), 8.01(1H,d,J=8.4Hz),8.09(1H,d,J=8.4Hz),8.52(1H,s),8.88(0.5H,s),8.91(0.5H,s),9.43-9.47 (3H,m),9.59(2H,s)
88	NMR(DMSO-d_6) δ :1.98-2.08(m,2H),3.07(s,3H),3.05-3.13(m,2H),3.15-3.22(m,2H),3.40-3.45 (m,2H),3.61-3.68(m,2H),4.99(s,2H),6.71(d,2H,J=8.8Hz),6.89(s,1H),7.20(d,2H,J=9.3Hz), 7.70(dd,1H,J=1.9Hz,8.8Hz),7.82(d,1H,J=8.8Hz),8.05(d,1H,J=1.5Hz),8.84-8.91(m,2H),8.95 (s,2H),9.25(s,2H)
89	NMR(DMSO-d_6) δ :1.80-1.89(m,2H),2.04(s,2H),2.26(s,1H),3.08(s,3H),3.48-3.58(m,4H),3.58-3.64(m,1H),3.65-3.78(m,3H),4.99(s,2H),6.72(d,0.6H,J=9.3Hz),6.74(d,1.4H,J=9.3Hz),6.86 (s,0.7H),6.88(s,0.3H),7.18(d,1.4H,J=8.8Hz),7.18(d,0.6H,J=8.9Hz),7.72(dd,1H,J=2.0Hz, 8.8Hz),7.82(d,1H,J=8.8Hz),8.08(d,0.3H,J=1.9Hz),8.11(d,0.7H,J=1.4Hz),8.62(s,0.7H),8.76 (s,0.3H),9.12(s,2H),9.26-9.32(m,1H),9.32-9.42(m,2H)
90	NMR(DMSO-d_6) δ :1.82-1.89(2H,m),3.42-3.46(2H,m),3.59-3.64(4H,m),3.83-3.87(2H,m),4.22 (2H,s),4.98(2H,s),6.69(2H,d,J=8.8Hz),7.03-7.09(2H,m),7.16(2H,m),7.60(1H,dd,J=1.6Hz, 8.4Hz),7.74(1H,dd,J=1.6Hz,8.4Hz),7.87(1H,s),8.00(1H,d,J=8.4Hz),8.09(1H,d,J=8.4Hz), 8.12-8.16(2H,m),8.38(1H,s),13.86(1H,s)
91	NMR(DMSO-d_6) δ :2.06-2.13(1H,m),2.28-2.42(1H,m),3.70(1.5H,s),2.72(1.5H,s),2.99-3.08 (2H,m),3.26-3.40(4H,m),3.62-3.76(2H,m),4.24(2H,s),5.02(2H,s),6.66(2H,d,J=9.2Hz),7.22 (2H,d,J=9.2Hz),7.66(1H,dd,J=1.6Hz,8.4Hz),7.73(1H,dd,J=1.6Hz,8.4Hz),7.89(1H,s),8.01 (1H,d,J=8.8Hz),8.08(1H,d,J=8.8Hz),8.38(1H,s),8.96-9.50(2H,br),11.24(1H,s)
92	NMR(DMSO-d_6) δ :1.98-2.05(2H,m),2.55(3H,s),2.89-3.00(4H,m),3.28-3.33(2H,m),3.52-3.55 (2H,m),3.64(3H,s),3.92(2H,s),5.01(2H,s),6.60(2H,d,J=8.8Hz),7.25(2H,d,J=8.8Hz),7.57 (1H,d,J=7.2Hz),7.81(1H,s),7.89-7.94(2H,m),8.00(1H,dd,J=2.0Hz,8.8Hz),8.51(1H,s),9.20 (2H,s)
93	NMR(DMSO-d_6) δ :2.00-2.10(2H,m),3.00-3.08(2H,m),3.08-3.16(2H,m),3.38-3.45(2H,m), 3.60-3.70(2H,m),4.24(2H,s),5.01(2H,s),6.68(2H,d,J=8.8Hz),7.21(2H,d,J=8.8Hz),7.65 (1H,dd,J=1.6Hz,8.8Hz),7.73(1H,dd,J=1.6Hz,8.8Hz),7.89(1H,s),8.01(1H,d,J=8.8Hz),8.08 (1H,d,J=8.8Hz),8.37(1H,s),9.33(4H,br),11.43(1H,br)
94	NMR(DMSO-d_6) δ :2.02-2.14(1H,m),2.25-2.35(1H,m),2.72(3H,d,J=4.9Hz),2.96-3.08(2H,m), 3.24-3.44(4H,m),3.59-3.74(2H,m),4.87(2H,s),6.62(2H,d,J=9.0Hz),7.18(2H,d,J=9.0Hz), 7.67-7.74(2H,m),7.91(1H,br s),7.98(1H,d,J=8.6Hz),8.07(1H,d,J=8.6Hz),8.33(1H,br s)

表２４

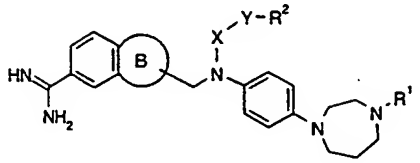
Ex	DATA
95	NMR(DMSO-d_6) δ :1.26(3H,t,J=6.8Hz),1.83-1.90(2H,m)3.33-3.37(2H,m),3.39-3.43(2H,m), 3.52-3.56(2H,m),3.62-3.66(2H,m),4.23(2H,q,J=6.8Hz),4.33(2H,s),4.93(2H,s),5.94(2H,s), 6.66(2H,d,J=9.2Hz),6.71(2H,d,J=6.4Hz),7.13(2H,d,J=9.2Hz),7.43(1H,dd,J=1.6Hz,8.8Hz), 7.69(1H,s),7.82-7.85(3H,m),8.06(2H,d,J=9.2Hz),8.13(1H,s),9.79(1H,s)
96	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.93-2.01(2H,m),2.42(3H,s),2.68-2.83(2H,m),2.95-3.03 (4H,m),3.50-3.53(2H,m),4.24(2H,q,J=7.2Hz),4.34(2H,s),4.95(2H,s),5.91(2H,s),6.61(2H,d, J=9.2Hz),7.16(2H,d,J=9.2Hz),7.46(1H,dd,J=1.6Hz,8.0Hz),7.71(1H,s),7.81-7.82(2H,m),7.85 (1H,d,J=8.0Hz),8.14(1H,s),9.77(1H,s)
97	NMR(DMSO-d_6) δ :1.27(3H,t,J=6.8Hz),2.00-2.04(2H,m),2.98-3.08(2H,m),3.08-3.17(2H,m), 3.38-3.45(2H,m),3.60-3.70(2H,m),4.24(2H,q,J=6.8Hz),4.36(2H,s),5.01(2H,s),6.69(2H,d,J= 8.8Hz),7.21(2H,d,J=8.8Hz),7.65(1H,dd,J=1.6Hz,8.8Hz),7.73(1H,dd,J=1.6Hz,8.8Hz),7.89 (1H,s),8.02(1H,d,J=8.8Hz),8.08(1H,d,J=8.8Hz),8.38(1H,s),9.37(4H,br),11.42(1H,br)
98	NMR(DMSO-d_6) δ :2.08-2.25(2H,m),2.67(3H,d),2.77(3H,d),3.00-3.15(2H,m),3.25-3.72(6H,m), 4.92(2H,s),6.62(2H,d),7.17(2H,d),7.28(1H,q),7.64(1H,d),7.71(1H,d),7.91(1H,s),7.97(1H,d), 8.04(1H,d),8.29(1H,s),10.45-10.60(1H,brs)
99	NMR(DMSO-d_6) δ :2.04-2.14(1H,m),2.22-2.34(1H,m),2.73(3H,d),2.78(6H,s),2.99-3.10(2H,m), 3.25-3.43(3H,m),3.56-3.92(3H,m),4.99(2H,s),6.63(2H,d),7.21(2H,d),7.65(1H,dd),7.72 (1H,dd),7.87(1H,s),8.00(1H,d),8.07(1H,d),8.85-9.35(1H,br),10.82-10.94(1H,brs),11.20-11.42(1H,brs)
100	NMR(DMSO-d_6) δ :2.04-2.12(1H,m),2.27-2.39(1H,m),2.71(1.5H,s),2.72(1.5H,s),2.98-3.08 (5H,m),3.23-3.42(4H,m),3.60-3.75(2H,m),4.58-4.88(2H,br),4.99(2H,s),6.65(2H,d,J=8.8Hz), 7.23(2H,d,J=8.8Hz),7.66(1H,dd,J=2.0Hz,8.4Hz),7.72(2H,dd,J=1.6Hz,8.4Hz),7.90(1H,s), 8.00(1H,d,J=8.8Hz),8.07(1H,d,J=8.8Hz),8.38(1H,s),11.09(1H,s)
101	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.1Hz),1.93-2.03(2H,m),2.52-2.58(3H,m),2.88-3.05(6H,m), 3.10-3.20(2H,m),4.08(2H,d,J=7.1Hz),5.07(2H,s),5.90(2H,s),6.53(2H,d,J=8.8Hz),7.07(2H,d, J=8.8Hz),7.49(1H,dd,J=1.5Hz,8.3Hz),7.69(1H,br s),7.77-7.83(3H,m),8.09(1H,s),9.74(1H,s)
102	NMR(DMSO-d_6) δ :2.04-2.15(1H,m),2.27-2.40(1H,m),2.71(3H,d,J=4.8Hz),2.94-3.11(2H,m), 3.25-3.47(4H,m),3.60-3.75(2H,m),3.91(3H,s),4.88(2H,s),6.62(2H,d,J=9.2Hz),7.18(2H,d, J=9.2Hz),7.73-7.80(2H,m),7.96(1H,s),8.00(1H,d,J=7.6Hz),8.08(1H,d,J=7.6Hz),8.43(1H,s), 10.65(1H,brs),11.31(1H,brs),11.63(1H,brs)
103	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.85-1.93(2H,m),2.34(3H,s),2.52-2.75(2H,m),3.32-3.35(4H,m),3.45-3.49(2H,m),3.65(3H,s),4.24(2H,q,J=7.2Hz),4.35(2H,s),4.98(2H,s),6.60 (2H,d,J=8.8Hz),7.16(2H,d,J=8.8Hz),7.57(1H,dd,J=1.2Hz,8.8Hz),7.82(1H,s),7.92-7.95 (2H,m),8.01(1H,dd,J=1.6Hz,8.8Hz),8.52(1H,s),9.17(2H,s)
104	NMR(DMSO-d_6) δ :2.02-2.15(1H,m),2.30-2.40(1H,m),2.67(3H,s),2.71(3H,d,J=4.9Hz),2.98-3.10(2H,m),3.24-3.44(4H,m),3.60-3.75(2H,m),3.92(3H,s),4.94(2H,s),6.63(2H,d,J=9.0Hz), 7.18(2H,d,J=9.0Hz),7.69(1H,dd,J=1.6Hz,8.7Hz),7.78(1H,dd,J=1.6Hz,8.7Hz),7.93(1H,brs), 8.01(1H,d,J=8.3Hz),8.08(1H,d,J=8.3Hz),8.45(1H,brs),10.65(1H,s),11.34(1H,brs),11.65 (1H,s)
105	NMR(DMSO-d_6) δ :1.76-1.86(2H,m),2.19(3H,s),2.35-2.42(2H,m),2.75(3H,s),3.32(6H,s), 3.37-3.44(2H,m),3.64(4H,s),4.93(2H,s),6.55(2H,d,J=9.1Hz),7.12(2H,d,J=9.1Hz),7.47-7.59(1H,m),7.80(1H,brs),7.91-8.03(3H,m),8.51(1H,s),9.17(1H,brs)
106	NMR(DMSO-d_6) δ :2.04-2.15(2H,m),2.25-2.35(1H,m),2.73(3H,d,J=4.3Hz),3.02-3.10(2H,m), 3.04(3H,s),3.25-3.75(6H,m),3.91(3H,s),5.00(2H,s),6.65(2H,d,J=9.1Hz),7.23(2H,d,J=9.1Hz) ,7.69(1H,dd,J=1.5Hz,8.3Hz),7.78(1H,dd,J=1.5Hz,8.3Hz),7.78(1H,dd,J=1.5Hz,8.3Hz),7.94(1H,brs),8.02(1H,d,J=8.6Hz),8.08(1H,d,J=8.6Hz),8.46(1H,brs),10.16(1H,brs),10.91(1H,brs)
107	NMR(DMSO-d_6) δ :1.23(3H,t,J=7.1Hz),1.91(2H,brs),2.54(3H,s),2.65(2H,brs),2.84(2H,brs), 2.93(2H,brs),3.06(2H,brs),3.64(3H,s),4.04(2H,q,J=7.0Hz),5.10(2H,s),6.47(2H,d,J=8.8Hz), 7.07(2H,d,J=8.8Hz),7.62(1H,dd,J=1.2Hz,8.6Hz),7.79(1H,brs),7.87-7.99(3H,m),8.46 (1H,brs),9.16(1H,brs)

表２５



Ex	R^1		X	Y	R^2
108	-C(=NH)-Me		$-SO_2-$	-4-Ph-	-COOH
109	-Me		$-SO_2-$	-4-Ph-	-COOH
110	-C(=NH)-Me		$-SO_2-$	-4-Ph-	-COOEt
111	-C(=NH)-Me		-CO-	-4-Ph-	-COOH
112	-Me		-CO-	-4-Ph-	-COOH
113	-C(=NH)-Me		$-SO_2-$	-3-Ph-	-COOH
114	-Me		$-SO_2-$	-3-Ph-	-COOH
115	-C(=NH)-Me		-CO-	-3-Ph-	-COOH
116	-COOEt		$-SO_2-$	$-CH_2-$	-COOH
117	$-CONH_2$		$-SO_2-$	$-CH_2-$	-COOH
118	-CONHMe		$-SO_2-$	$-CH_2-$	-COOH
119	$-CON(Me)_2$		$-SO_2-$	$-CH_2-$	-COOH
120	-Me		-CO-	$-CH_2-$	-COOH
121	-Me		-CO-	$-CH_2CH_2-$	-COOH
122	-Me		$-SO_2-$	$-CH_2-$	-COOH
123	-Me		$-SO_2-$	$-CH_2-$	-COOEt
124	-Me		$-SO_2-$	$-CH_2CH_2-$	-COOH
125	-C(=HN)-Me		-CO-	$-CH_2-$	-COOH
126	-C(=HN)-Me		-CO-	$-CH_2CH_2-$	-COOH
127	-C(=HN)-Me		$-SO_2-$	$-CH_2-$	-COOH
128	-C(=HN)-Me		$-SO_2-$	$-CH_2-$	-COOEt
129	-C(=HN)-Me		$-SO_2-$	$-CH_2CH_2-$	-COOH

表２６



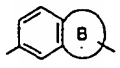
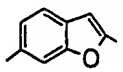
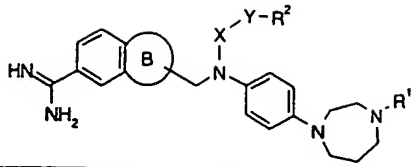
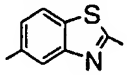
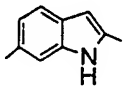
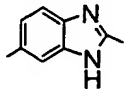
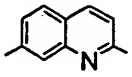
Ex		R^1	X	Y	R^2
130		-Me	-CO-	$-CH_2-$	-COOH
131		-Me	-CO-	$-CH_2CH_2-$	-COOH
132		-Me	$-SO_2-$	$-CH_2-$	-COOH
133		-Me	$-SO_2-$	$-CH_2-$	-COOEt
134		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
135		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
136		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
137		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
138		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
139		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH

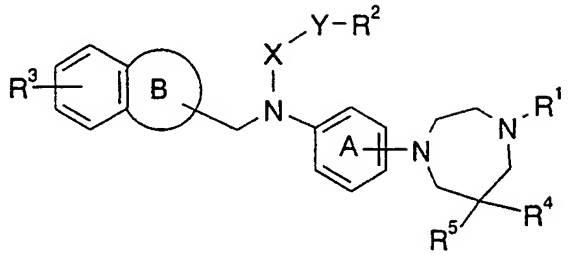
表２７



Ex	B	R^1	X	Y	R^2
140		-Me	-CO-	$-CH_2-$	-COOH
141		-Me	-CO-	$-CH_2CH_2-$	-COOH
142		-Me	$-SO_2-$	$-CH_2-$	-COOH
143		-Me	$-SO_2-$	$-CH_2-$	-COOEt
144		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
145		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
146		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
147		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
148		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
149		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
150		-Me	-CO-	$-CH_2-$	-COOH
151		-Me	-CO-	$-CH_2CH_2-$	-COOH
152		-Me	$-SO_2-$	$-CH_2-$	-COOH
153		-Me	$-SO_2-$	$-CH_2-$	-COOEt
154		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
155		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
156		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
157		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
158		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
159		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
160		-Me	-CO-	$-CH_2-$	-COOH
161		-Me	-CO-	$-CH_2CH_2-$	-COOH
162		-Me	$-SO_2-$	$-CH_2-$	-COOH
163		-Me	$-SO_2-$	$-CH_2-$	-COOEt
164		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
165		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
166		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
167		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
168		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
169		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
170		-Me	-CO-	$-CH_2-$	-COOH
171		-Me	-CO-	$-CH_2CH_2-$	-COOH
172		-Me	$-SO_2-$	$-CH_2-$	-COOH
173		-Me	$-SO_2-$	$-CH_2-$	-COOEt
174		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
175		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
176		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
177		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
178		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
179		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH

請 求 の 範 囲

1．下記一般式（Ｉ）で示されるヘキサヒドロ－１，４－ジアゼピン誘導体又はその製薬学的に許容される塩。



（Ｉ）

（但し、式中の記号は、下記の意味を有する。

Ａ：フェニレン又はピリジレン基（これらは置換基を有してしてもよい）、

Ｂ：５乃至６員のアリール又はヘテロアリールを形成する、

Ｘ：－ＣＯ－、－ＣＯＮＨ－、－ＣＳＮＨ－、－SO_2－、－SO_2ＮＨ－、又は式－SO_2Ｎ（－低級アルキル）－で示される基、

Ｙ：結合又は低級アルキレン基、

R^1：水素原子、低級アルキル、－Ｌ－アリール、Ｌ－ヘテロアリール、－Ｌ－ＣＯＯ－R^6、－Ｌ－ＣＯＮ（－R^6）－R^7、－Ｃ（＝ＮＨ）－NH_2又は－Ｃ（＝ＮＨ）－低級アルキル基、

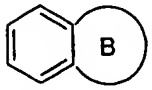
R^2：水素原子、－Ｏ－低級アルキル、－ＣＯＯＨ、－ＣＯＯ－低級アルキル、－$CONH_2$、－ＣＯＮＨ－低級アルキル、－ＣＯＮ－ジ－低級アルキル基、或いは、アリール又はヘテロアリール基（これらは置換基を有していてよい）、

R^3：アミジノ基又は生体内でアミジノ基に転化されうる基、

R^4，R^5：同一又は異なって、水素原子又は低級アルキル基、

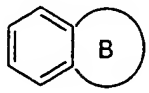
R^6，R^7：同一又は異なって、水素原子又は低級アルキル基、

Ｌ：結合又は低級アルキレン基）

2．環  が、ナフタレン又はベンゾフラン

である請求の範囲１記載のヘキサヒドロ－１，４－ジアゼピン誘導体又はその製薬学的に許容される塩。

３．R^4及びR^5が共に水素原子である請求の範囲２記載のヘキサヒドロ－１，４－ジアゼピン誘導体又はその製薬学的に許容される塩。

４．環  が、ナフタレンであり、

Aがフェニレン基（該フェニレン基はハロゲン原子、アミノ、シアノ、ニトロ、－OH、－COOH、低級アルキル、－O－低級アルキル、又は－COO－低級アルキル基から選択される置換基を有していてもよい）又はピリジレン基であり、R^3がアミジノ基である請求の範囲３記載のヘキサヒドロ－１，４－ジアゼピン誘導体又はその製薬学的に許容される塩。

５．Aがフェニレン又はピリジレン基であり、Xが－CO－、－CSNH－、－SO_2－又は－SO_2NH－で示される基であり、R^1が水素原子、低級アルキル、ピリジル又は－C（＝NH）－CH_3基であり、R^2が水素原子、－COOH、－COO－低級アルキル又はテトラゾリル基である請求の範囲４記載のヘキサヒドロ－１，４－ジアゼピン誘導体又はその製薬学的に許容される塩。

６．N－〔４－（４－アセトイミドイルヘキサヒドロ－１H－１，４－ジアゼピン－１－イル）フェニル〕－N－〔（７－アミジノ－２－ナフチル）メチル〕アセトアミド、

エチル　〔N－〔４－（４－アセトイミドイルヘキサヒドロ－１H－１，４－ジアゼピン－１－イル）フェニル〕－N－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕アセテート、

エチル　N－〔N－〔４－（４－アセトイミドイルヘキサヒドロ－１H－１，４－ジアゼピン－１－イル〕フェニル〕－N－〔（７－アミジノ－２－ナフチル）メチル〕スルファモイル〕グリシネート、

エチル　N－〔４－（４－アセトイミドイルヘキサヒドロ－１H－１，４－ジアゼピン－１－イル）フェニル〕－N－〔（７－アミジノ－２－ナフチル）

メチル〕マロナメート、

〔N－〔6－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）－3－ピリジル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕スルファモイル〕アセティックアシッド、

〔N－〔4－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）フェニル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕スルファモイル〕アセティックアシッド、

N－〔4－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）フェニル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕スクシナミックアシッド、

エチル N－〔4－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）－3－ピリジル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕マロナメート、

エチル N－〔4－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）－3－ピリジル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕スクシナメート、

N－〔4－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）フェニル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕チオアミドアセティックアシッド、

N－〔4－（4－アセトイミドイルヘキサヒドロ－1H－1，4－ジアゼピン－1－イル）－3－ピリジル〕－N－〔（7－アミジノ－2－ナフチル）メチル〕スクシナミックアシッド、

又はこれらの製薬学的に許容される塩。

7．請求の範囲1に記載されるヘキサヒドロ－1，4－ジアゼピン誘導体又はその製薬学的に許容される塩、及び製薬学的に許容される担体を含んでなる医薬組成物。

8．活性化血液凝固第X因子阻害剤である請求の範囲7に記載の医薬組成物。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/03267

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07D243/08, C07D401/04, C07D405/12, A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07D243/08, C07D401/04, C07D405/12, A61K31/55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
EA	JP, 10-017549, A (Banyu Pharmaceutical Co., Ltd.), 20 January, 1998 (20. 01. 98) (Family: none)	1-8
A	WO, 94/02472, A1 (Taisho Pharmaceutical Co., Ltd.), 3 February, 1994 (03. 02. 94), Claims & EP, 649843, A1 & US, 5478945, A & AU, 9345135, A	1-8
A	JP, 5-208946, A (Daiichi Pharmaceutical Co., Ltd.), 20 August, 1993 (20. 08. 93), Refer to all references & EP, 540051, A1 & TW, 210998, A & CN, 1072677, A & US, 5576343, A	1-8
A	JP, 59-139357, A (Torii & Co., Ltd.), 10 August, 1984 (10. 08. 84), Refer to all references & DE, 3402628, A1 & GB, 2134901, A & FR, 2540118, A & US, 4634783, A	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October, 1998 (20. 10. 98)	27 October, 1998 (27. 10. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告

国際出願番号　PCT／JP98／03267

A.　発明の属する分野の分類（国際特許分類（IPC））

Int. Cl⁶　C07D243／08, C07D401／04, C07D405／12, A61K31／55

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl⁶　C07D243／08, C07D401／04, C07D405／12, A61K31／55

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS (STN), REGISTRY (STN)

C.　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
EA	JP, 10－017549, A（萬有製薬株式会社）20.1月.1998 (20.01.98) （ファミリーなし）	1－8
A	WO, 94／02472, A1（大正製薬株式会社）3.2月.1994 (03.02.94)　請求の範囲 & EP, 649843, A1　& US, 5478945, A　& AU, 9345135, A	1－8
A	JP, 5－208946, A（第一製薬株式会社）20.8月.1993 (20.08.93)　全文献参照 & EP, 540051, A1　& TW, 210998, A　& CN, 1072677, A & US, 5576343, A	1－8

☒ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」先行文献ではあるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日 20. 10. 98	国際調査報告の発送日　27.10.98
国際調査機関の名称及びあて先 日本国特許庁（ISA／JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	特許庁審査官（権限のある職員） 横尾　俊一　4C　7822 電話番号　03－3581－1101　内線　3453

様式PCT／ISA／210（第2ページ）（1992年7月）

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９８／０３２６７

Ｃ（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Ａ	ＪＰ，５９－１３９３５７，Ａ（鳥居薬品株式会社）10.8月.1984 (10.08.84)　全文献参照 & DE,3402628,A1　& GB,2134901,A　& FR,2540118,A & US,4634783,A	１－８

様式ＰＣＴ／ＩＳＡ／２１０（第２ページの続き）（１９９２年７月）

(19) Europäisches Patentamt
European Patent Office
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(11) EP 1 000 936 A1

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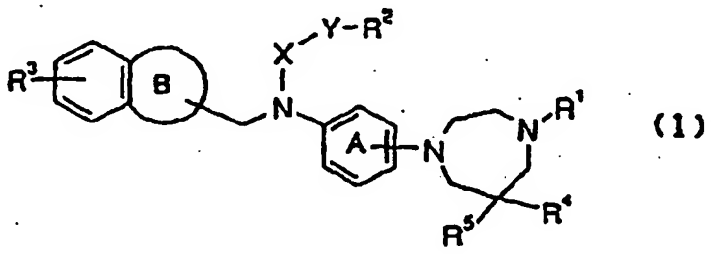
(54) NOVEL HEXAHYDRO-1,4-DIAZEPINE DERIVATIVES OR SALTS THEREOF

(57)



(1)

Hexahydro-1,4-diazepine derivatives represented by general formula (I); pharmaceutically acceptable salts thereof; and drugs containing the same as the active ingredient, such as activated blood coagulation factor X inhibitor, wherein A: phenylene, pyridylene, or the like; B: a 5- or 6-membered aryl or heteroaryl ring; X: -CO-, -CONH-, -CSNH-, $-SO_2-$, $-SO_2NH-$, or the like; Y: a bond or alkylene; R^1: hydrogen, alkyl, -Y-(hetero)aryl, or the like; R^2: hydrogen, alkoxy, -COOH, or the like; R^3: amidino or a group capable of being converted into amidino; and R^4, R^5: each independently hydrogen or lower alkyl.

EP 1 000 936 A1

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Description

Technical Field:

[0001] The present invention relates to hexahydro-1,4-diazepine derivatives or their salts which are useful as drugs, especially as an activated blood coagulation factor X inhibitor.

Background of the Invention:

[0002] Recently, thromboembolic disorders, such as myocardial infarction, cerebral thrombosis and peripheral arteriothrombosis, are increasing year by year with the popularization of Western life-styles and the increase in aged population, and there is much increasing social demand for the treatment of such disorders.

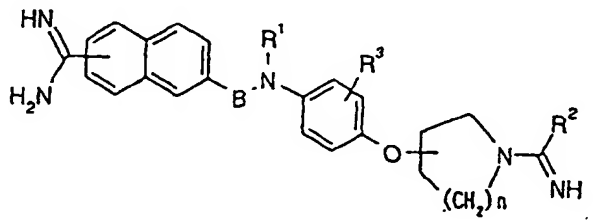
[0003] Anticoagulant therapy as well as adenolytic therapy and antiplatelet therapy is a part of medical therapy for treatment and prevention of thrombosis (*Sogo Rinsho*, 41: 2141-2145, 1989). In particular, anticoagulants for prevention of thrombosis indispensably require high safety for long-term administration and the ability of surely and appropriately expressing the anticoagulation activity.

[0004] However, the anticoagulating ability of warfarin potassium, which is only one oral anticoagulant now being popularly used in the world, is difficult to control because of the characteristic of itself based on the action and the mechanism thereof (*J. Clinical Pharmacology*, 32, 196-209, 1992; and *N. Eng. J. Med.*, 324 (26), 1865-1875, 1991), and the drug is extremely difficult to use in clinics.

[0005] It is known that thrombin acts to convert fibrinogen into fibrin in the final stage of coagulation, while deeply participating in the activation and the coagulation of platelets. At present, however, no oral thrombin inhibitor is commercially available because of its low bioavailability in oral administration and of its low safety (*Biomed. Biochim. Acta*, 44, 1201-1210, 1985).

[0006] On the other hand, the activated blood coagulation factor X is a key enzyme existing in the junction of intrinsic and extrinsic coagulation cascade reactions, and inhibiting this factor is more efficient than thrombin inhibition, and could bring about specific inhibition of coagulation systems (*THROMBOSIS RESEARCH* (19), 339-349, 1980).

[0007] As compounds having the ability of inhibiting the activated blood coagulation factor X, known are amidinonaphthylbenzene derivatives or their salts (JP-A-5-208946; *Thrombosis Haemostasis*, 71 (3), 314-319, 1994; *Thrombosis Haemostasis*, 72 (3), 393-396, 1994); and WO96/16940 discloses amidinonaphthyl derivatives of the following general formula or their salts.



[In the formula, B represents a lower alkylene group, etc.; R^1 represents a hydrogen atom or a group of a formula, -A-W-R^4 [where A represents -CO-, -SO_2-, etc.; W represents a single bond or an -NR^5- group (where R^5 represents a hydrogen atom, a -$CONH_3$ group, etc.); R^4 represents an optionally-substituted lower alkyl group, etc.]; R^2 represents a lower alkyl group; R^3 represents a hydrogen atom, a halogen atom, etc.; and n = 0 or 1.]

[0008] As so mentioned above, inhibitors for the activated blood coagulation factor X are more effective than thrombin inhibitors in anticoagulant therapy, and are expected to bring about specific inhibition of coagulation systems.

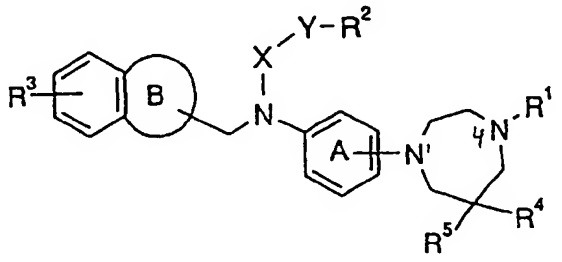
[0009] Accordingly, it is desired to create selective activated blood coagulation factor X inhibitors, which are different from the known compounds noted above in the chemical structure, can be orally administered and are more effective.

Disclosure of the Invention:

[0010] We, the present inventors have found that hexahydro-1,4-diazepine derivatives of the following general formula (I) or their salts, of which the chemical structure is characterized in that an amidinonaphthylmethyl group or the

like is bonded to a phenyl group or a pyridyl group via a nitrogen atom and that the phenyl group or the pyridyl group is directly bonded to the nitrogen atom of the hexahydro-1,4-diazepine ring, have an excellent activity of inhibiting the activated blood coagulation factor X, and have completed the present invention.

[0011] Specifically, the invention relates to hexahydro-1,4-diazepine derivatives of the following general formula (I) or their salts, as well as pharmaceutical compositions, especially, activated blood coagulation factor X inhibitors comprising them as active ingredients:



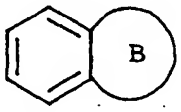
(I)

(In the formula, the symbols have the following meanings:

A: a phenylene or pyridylene group (which may be substituted),
B: forming a 5- or 6-membered aryl or heteroaryl,
X: a group of formula, -CO-, -CONH-, -CSNH-, - SO_2-, -SO_2NH-, or -SO_2N(-lower alkyl)-,
Y: a bond or a lower alkylene group,
R^1: a hydrogen atom, or a lower alkyl, -L-aryl, -L-heteroaryl, -L-COO-R^5, -L-CON(-R^6)-R^7, -C(=NH)-NH_2, or -C(=NH)-lower alkyl group,
R^2: a hydrogen atom, an -O-lower alkyl, -COOH, - COO-lower alkyl, -$CONH_2$, -CONH-lower alkyl, or -CON-di-lower alkyl group, or an aryl or heteroaryl group (which may be substituted),
R^3: an amidino group or a group capable of being converted into an amidino group in a living body,
R^4, R^5: a hydrogen atom or a lower alkyl group, which may be the same or different,
R^6, R^7: a hydrogen atom or a lower alkyl group, which may be the same or different, and
L: a bond, or a lower alkylene group.)

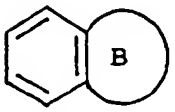
[0012] The structure of the compounds of the invention is obviously different from that of the known compounds noted above in the basic skeleton, in which hexahydro-1,4-diazepinylphenyl (or hexahydro-1,4-diazepinylpyridyl) is bonded to the amidinonaphthylmethyl group via a nitrogen atom in the former, while the pyrrolidinyl- (or piperidinyl)oxyphenyl group is bonded to the amidinonaphthylmethyl group via a nitrogen atom in the latter.

[0013] Of the compounds of the invention, preferred are hexahydro-1,4-diazepine derivatives of the general formula (I), wherein the ring



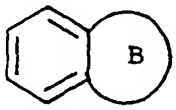
is naphthalene or benzofuran, or their salts, or hexahydro-1,4-diazepine derivatives where R^4 and R^5 are each a hydrogen atom, or their salts.

[0014] More preferred are hexahydro-1,4-diazepine derivatives of the general formula (I), wherein the ring



is naphthalene; A is a phenylene group (the phenylene group may be substituted with a substituent selected from a halogen atom, or an amino, cyano, nitro, -OH, -COOH, lower alkyl, -O-lower alkyl, or -COO-lower alkyl group) or a pyridyl group; R^3 is an amidino group; and R^4 and R^5 are each a hydrogen atom, or their salts.

[0015] Of the compounds of the invention, particularly preferred are hexahydro-1,4-diazepine derivatives of the general formula (I), wherein the ring



is naphthalene; A is a phenylene or pyridylene group; X is a group of formula, -CO-, -CSNH-, $-SO_2-$, or $-SO_2NH-$; R^1 is a hydrogen atom, or a lower alkyl, pyridyl, or - $C(=NH)-CH_3$ group; R^2 is a hydrogen atom, or a -COOH, - COO-lower alkyl, or tetrazolyl group; R^3 is an amidino group; and R^4 and R^5 are each a hydrogen atom, or their salts.

[0016] Of the compounds of the invention, most preferred are those enumerated below:

N-[4-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]acetamide,
Ethyl [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetate,
Ethyl N-[N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]glycinate,
Ethyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]malonamate,
[N-[6-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetic acid,
[N-[4-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetic acid,
N-[4-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]succinamic acid,
Ethyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]malonamate,
Ethyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]succinamate,
N-[4-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]thioamidoacetic acid, and
N-[4-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]succinamic acid.

[0017] Now, the compounds (I) of the invention are described in detail hereunder.

[0018] Unless otherwise specifically indicated, the term "lower" in the definition of the groups in the general formulae as referred to in the present specification means a linear or branched carbon chain having from 1 to 6 carbon atoms.

[0019] Accordingly, the "lower alkyl group" is an alkyl group having from 1 to 6 carbon atoms, including, for example, methyl, ethyl, propyl, butyl, pentyl and hexyl groups and their structural isomers such as isopropyl group, etc. Preferably, it is an alkyl group having from 1 to 4 carbon atoms, more preferably, a methyl or ethyl group.

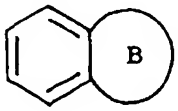
[0020] The "lower alkylene group" is a linear or branched alkylene group having from 1 to 6 carbon atoms, including, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene groups and their structural isomers. Preferably, it is an alkylene group having from 1 to 3 carbon atoms, more preferably a methylene or ethylene group.

[0021] The "aryl" is an aromatic ring having from 6 to 14 carbon atoms, which may be substituted, including, for example, benzene, naphthalene, anthracene and phenanthrene groups. Preferably, it is benzene or naphthalene.

[0022] The "heteroaryl" is a 5- or 6-membered aromatic ring containing from one to four N, O or S atoms, or a bicy-

cle having 5- or 6-membered aromatic rings fused with each other, each of which may be substituted, including, for example, furan, pyrrole, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, tetrazole, and naphthyridine. Most preferably, B is furan, R^1 is a pyridyl group, and R^2 is a tetrazolyl group.

[0023] The ring



includes, for example, naphthalene, benzofuran, indole, benzothiophene, benzoimidazole, benzoxazole, benzothiazole, quinoline, and quinazoline. Preferably, it is benzoxazole or benzofuran.

[0024] The substituent for the "aryl group" or "heteroaryl group", or the substituent for the "phenylene or pyridylene group", is any substituent which is usually used as the substituent for aryl or heteroaryl, including, example, lower alkyl (the lower alkyl may be substituted with from one to four substituents selected from the group consisting of a halogen atom, and -O-lower alkyl, -COOH, amino, -NH-lower alkyl, and -N-di-lower alkyl groups), -OH, -O-lower alkyl, -COOH, -COO-lower alkyl, a halogen atom, amino, cyano, nitro, -NH-lower alkyl, and -N-di-lower alkyl groups; and the substituent for the phenylene group includes, for example, -S-lower alkyl, -SO-lower alkyl, $-SO_2$-lower alkyl, $-CONH_2$, and -O-lower alkylene-O- groups. These groups may further contain from one to three substituents. Preferably, it is a substituent selected from a halogen atom, and amino, cyano, nitro, -OH, -COOH, lower alkyl, -O-lower alkyl, and -COO-lower alkyl groups.

[0025] The "halogen atom" includes, for example, F, Cl, Br, and I atoms.

[0026] The "group capable of being converted into an amidino group in a living body" means a so-called prodrug group, which is an amidino group having -OH, -COO-lower alkyl group, or the like substituted thereon and can be removed under physiological conditions to form an amidino group. It includes, for example, $-C(-NH_2)=N-OH$, $-C(-NH_2)=N-COO$-lower alkyl, and other groups known in this art.

[0027] Depending on the type of the substituents therein, the compounds of the invention may include geometrical isomers and tautomers of cis-trans (or (E)-form and (Z)-form) ones based on the double bond therein, and optical isomers of (R)-form and (S)-form ones based on the asymmetric carbon atom therein. The invention shall encompass all of mixtures and isolated ones of those geometrical isomers, tautomers and optical isomers.

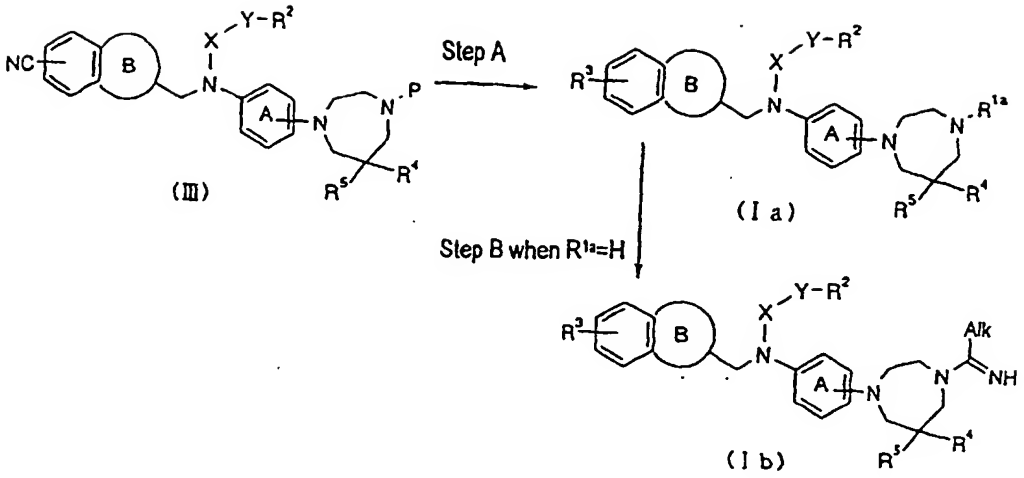
[0028] The compounds (I) of the invention may form acid-addition salts, and even salts with bases, depending on the type of the substituents therein. Those salts shall be pharmaceutically acceptable ones, and may include, for example, acid-addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; or with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, toluene-sulfonic acid, aspartic acid, glutamic acid, etc.; as well as salts of inorganic bases of sodium, potassium, magnesium, calcium, aluminum etc., or with organic bases such as methylamine, ethylamine, ethanolamine, lysine, ornithine, etc.; ammonium salts, etc. Of these are preferred hydrochlorides, hydrobromides, sulfates, phosphates, fumarates, maleates, citrates, methanesulfonates, ethanesulfonates, propanesulfonates, and toluenesulfonates.

[0029] The invention further encompasses various hydrates, solvates and polymorphic crystals of the compounds (I) and their salts of the invention.

[0030] Naturally, the invention is not limited to the compounds described in the Examples to be mentioned hereunder, but shall include any and every type of hexahydro-1,4-diazepine derivatives of the general formula (I) or their salts.

(Production Method)

[0031] One typical method for producing the compounds (I) of the invention is mentioned below.



(In the formulae, A, B, R^2, R^3, R^4, X and Y have the same meanings as above; Alk represents a lower alkyl group; R^{1a} represents a hydrogen atom or a pyridyl group; and P represents a pyridyl group or an amino-protecting group.)

[0032] The amino-protecting group of P is not specifically limited, and may be any and every group generally used for protecting amino groups. For example, it includes - COO-lower alkyl, -COO-lower alkyl-aryl, acyl, lower alkyl, -lower alkyl-aryl, $-SO_2$-lower alkyl groups, etc.

[Step A]

[0033] Of the compounds of the invention, those (Ia) where R^1 is a hydrogen atom or a pyridyl group can be produced according to any of the methods (1) to (3) mentioned below.

(1) A method of converting a nitrile into an imidate, followed by condensing it with an amine:

[0034] A nitrile compound (III) is reacted with an alcohol such as methanol, ethanol or the like in the presence of hydrochloric acid gas at -40 to 0°C to be converted into an imidate, which is then reacted with an amine or amine salt, such as ammonia, ammonium carbonate, ammonium chloride, ammonium acetate or the like. As a solvent, a solvent which is effective for the reaction, or an inert solvent is used. The inert solvent includes tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), benzene, toluene, xylene, ethyl acetate, acetone, acetonitrile, dichloromethane, dichloroethane, chloroform, methanol, ethanol, isopropanol, mixtures thereof, etc.

(2) A method of converting a nitrile into a thioimidate via a thioamide, followed by condensing it with an amine:

[0035] First, a nitrile compound (III) is reacted with hydrogen sulfide in the presence of an organic base such as methylamine, triethylamine, pyridine, picoline, or the like, or is reacted with O,O-diethyl dithiophosphate in the presence of hydrogen chloride, thereby converting it into a thioamide. Next, the resulting thioamide is reacted with a lower alkyl halide such as methyl iodide, ethyl iodide, or the like, thereby converting it into a thioimidate, which is then reacted with an amine or amine salt, such as ammonia, ammonium carbonate, ammonium chloride, ammonium acetate, or the like. As a solvent, the above-described inert solvent is used.

(3) A method of directly adding an amine, an amine salt, a metal amide, or a Grignard reagent to a nitrile:

[0036] To a nitrile compound (III), added is any reagent of ammonia, ammonium chloride combined with ammonia, ammonium thiocyanate, an alkylammonium thiocyanate, $MeAl(Cl)NH_2$, $NaNH_2$, $(CH_3)_2NMgBr$, or the like. The reaction can be carried out in an inert solvent such as that mentioned above or in the absence of a solvent. A base such as sodium hydride or an acid such as aluminum chloride, p-toluenesulfonic acid, etc. may be added as a catalyst, whereby the reaction may be greatly promoted. The reaction may be effected with cooling, or at room temperature, or under heating.

[0037] In the reaction of converting the nitrile into an amidino group, the amino-protecting group of P could not be removed as the case may be. In that case, the protecting group may be removed in any suitable method for further removing it to obtain the compound (Ia) of the invention.

[0038] Where the compound (III) has a -COO-alkyl group bonded thereto, the -COO-alkyl group may be converted into a $-CONH_3$ group during the amidination.

[Step B]

[0039] Of the compounds of the invention, those (Ib) where R^1 is a -C(=NH)-lower alkyl group can be synthesized by reacting the compound (Ia) of the invention, which is produced in the previous first step and which has a secondary amino group (R^{1a} = H) with an imidate compound in the presence of a base.

[0040] This reaction may be effected with cooling or under heating, in which is usable the above-described inert solvent. As the base, usable are organic bases such as N-methylmorpholine, triethylamine, trimethylamine, pyridine, picoline, lutidine, dimethylaniline, etc. and inorganic bases such as sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, etc.

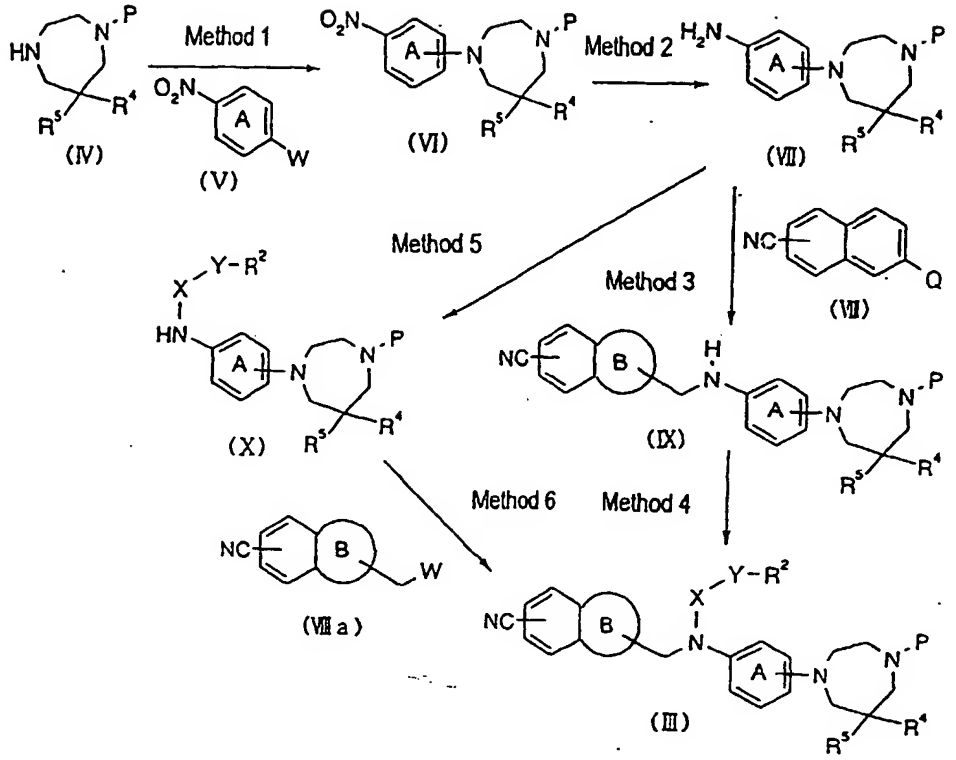
[0041] Where the compound (Ib) has a -COO-alkyl group bonded thereto, the group may be converted into a carboxyl group through hydrolysis under basic, acidic or neutral conditions, as the case may be.

[0042] In the hydrolysis, employable is a base such as sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide or the like under the basic conditions; an acid such as hydrochloric acid, sulfuric acid, Lewis acids, e.g., boron trichloride, p-toluenesulfonic acid, or the like under the acidic conditions; and a halide such as lithium iodide, lithium bromide, or the like, or an alkali metal salt of thiol or selenol, or iodotrimethylsilane, an enzyme such as esterase, or the like under the neutral conditions.

[0043] The reaction is effected generally at room temperature using an inert solvent such as that mentioned above, but in some cases, it requires cooling or heating the reaction system. The conditions may be suitably determined in any ordinary manner.

(Methods for Producing Starting Compounds)

[0044] Typical methods for producing starting compounds for the compounds (I) of the invention are mentioned below.



(In the formulae, A, B, R^2, R^4, R^5, X, Y and P have the same meanings as above; W represents a halogen atom or an organic sulfonic acid residue; Q represents an aldehyde group or a group of formula, $-CH_2-W$; and P' represents P or a hydrogen atom.)

Method 1:

[0045] This is to react a hexahydro-1,4-diazepine derivative (IV) with a nitrobenzene or nitropyridine derivative (V) to give a compound (VI). This reaction is the same as ordinary substitution reaction, and may be effected in no solvent or in an inert organic solvent such as that mentioned above, at room temperature or under heating, or even under heating for reflux, optionally in the presence of an inorganic base such as that mentioned above. When P' is a hydrogen atom, a similar substitution reaction is further carried out by using chloropyridine, etc. to synthesize a compound (VI) where P is a pyridyl group. If desired, an amino-protecting group may be introduced into the compound formed herein, in any suitable method to give a compound (VI) where P is the amino-protecting group.

Method 2:

[0046] This is to obtain an amine compound (VII) from the nitro compound (VI). This reaction may be ordinary reduction, for which, for example, employed is method of using a metal such as zinc, tin or the like; a method of using a metal hydride such as $LiAlH_4$ or the like; or a catalytic reduction method of using palladium-carbon or the like. These methods may be effected in an inert solvent such as that mentioned above, at room temperature or under heating.

Method 3:

[0047] This is ordinary N-alkylation.

(i) Where the compound (VIII) is an alkyl halide or alkyl sulfonate:

[0048] The reaction is effected by stirring the compound (VII) and a reaction-corresponding amount of a compound (VIII) in an inert solvent such as that mentioned above with cooling or under heating. To promote the reaction, it is desirable to add a base such as that mentioned above.

(ii) Where the compound (VIII) is an aldehyde:

[0049] The reaction is reductive amination of reacting the compound (VII) with a corresponding aldehyde (VIII) and a reducing agent. As the reducing agent, for example, employable is any of sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, etc. This reaction may be effected in an alcohol or an inert solvent such as that mentioned above while stirring with cooling or under heating (for reflux).

Method 4:

[0050] Starting compounds (III) can be produced according to any of the methods (a) to (c) mentioned below.

(a) Method for producing amide compounds (IIIa):

[0051] Of the starting compounds (III), amide compounds (IIIa) where X is -CO- can be synthesized through acylation of an amine (IX) with an active derivative of a carboxylic acid (for example, acid chloride, etc.).

[0052] Alternatively, amide compounds (IIIa) can also be synthesized through acylation of an amine (IX) and a carboxylic acid in the presence of a condensing agent. As the condensing agent, for example, favorably employed is any of N,N-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-(N,N-dimethylamino)propyl)carbodiimide, carbonyldiimidazole, etc. In general, the reaction may be effected in an inert solvent such as that mentioned above, with cooling or at room temperature and depending on the type of the acylation, the reaction is effected under anhydrous conditions. Also, the reaction may be effected in the presence of a base such as that mentioned above or using the base as the solvent, thereby promoting the reaction.

(b) Method for producing urea compounds (IIIb):

[0053] Of the starting compounds (III), urea compounds (IIIb) where X is -CONH- can be synthesized by reacting an amine (IX) with an isocyanate derivative, or by reacting the amine (IX) with phosgene, diphosgene, triphosgene, or the like to give a carbamoyl chloride, followed by further reacting it with an amine derivative.

[0054] This reaction may be effected in an inert solvent such as that mentioned above with cooling or under reflux. The solvent may be suitably selected, depending on the type of the reaction.

[0055] The reaction may be effected in the presence of a base such as that mentioned above or using the base as the solvent, thereby promoting the reaction.

(c) Method for producing sulfonamide compounds or sulfamide compounds (IIIc):

[0056] Of the starting compounds (III), sulfonamide compounds or sulfamide compounds (IIIc) where X^1 is $-SO_2-$ or $-SO_2NH-$ can be synthesized by reacting the amine (IX) with a sulfonyl halide derivative or a sulfonic acid anhydride, generally in the presence of a base such as that mentioned above. This reaction may be effected in an inert solvent such as that mentioned above with cooling or under reflux. The solvent may be suitably selected, depending on the type of the reaction.

Method 5:

[0057] When X of the compound (VII) is a group of -CO-, - CONH-, $-SO_2-$, or $-SO_2NH-$, the compound (X) can be synthesized in a similar manner to that in the Methods 4(a) to (c) noted above. Regarding the reaction conditions including the reaction temperature and the solvent to be used, etc. referred to are those for the Methods 4(a) to (c) noted above.

Method 6:

[0058] In this method, the reaction of the compound (VIIIa) with the compound (X) to give compounds (III) is the same as that in the Method 3(i) noted above. Regarding the reaction conditions including the reaction temperature and

the solvent to be used, etc. referred to are those for the Method 3(i) noted above.

[0059] The starting compounds for use in the invention may also be produced through any other known alkylation,, oxidation, reduction and hydrolysis by combining them in any manner well known to those skilled in the art. For alkylation, for example, a sulfonamide compound may be reacted with a reaction-equivalent amount or an excess amount of an alcohol (e.g., methanol, ethanol, etc.) with stirring them in the presence of triphenylphosphine and diethyl azocarboxylate, in an inert solvent such as that mentioned above at room temperature or under heating to obtain alkyl-substituted sulfonamide compounds.

[0060] The compounds of the invention thus produced in the manner noted above may be isolated and purified in any known method of, for example, extraction, precipitation, fractional chromatography, fractional crystallization, recrystallization or the like, and may be formed into desired salts through ordinary salt formation.

[0061] Of the compounds of the invention, those having an asymmetric carbon atom may include optical isomers, which may be resolved in any ordinary method of, for example, fractional crystallization of recrystallizing them with suitable salts, column chromatography or the like.

Industrial Applicability:

[0062] The compounds of the invention specifically inhibit the activated blood coagulation factor X, and have a strong anticoagulation activity. Accordingly, the compounds are useful as anticoagulants or as drugs for preventing and treating disorders to be induced by thrombi or exboli. The diseases for which the compounds of the invention are effective include those in cerebrovascular disorders such as cerebral infarction, cerebral thrombosis, cerebral embolism (*N Engl J Med.* 333, 1588-1593, 1995), acute and chronic myocardial infarction, unstable angina (*Thromb Haemost*, 74, 640-645, 1995), those in ischemic cardiopathy such as coronary thrombolysis, etc. (*Cardiovasc Res*, 28, 78-85, 1994; *J Am Coll Cardiol*, 28, 1858-1865, 1996), peripheral arterio-occlusion (*Fibrinolysis*, 7, 195-202, 1993), deep vein thrombosis (*Thromb Haemost*, 65, 257-262, 1991; *Thromb Res*, 71, 317-324, 1993), disseminated intravascular coagulation syndrome (*Thromb Haemost*, 72, 393-396, 1994), thrombophilia after artificial vasoformation and after artificial valvoplasty, re-occlusion and re-constriction after coronary bypass operation (*Circulation*, 84, 1741-1748, 1991), re-occlusion and re-constriction after PTCA (*Circulation*, 89, 1262-1271, 1994; *Circulation*, 93, 1542-1548, 1996), thrombophilia during extracorporeal circulation (*Thromb Haemost*, 74, 635-639, 1995), etc. Based on their activity to inhibit the activated blood coagulation factor X and their activity to inhibit the growth of influenza viruses, the compounds of the invention are expected to be usable for preventing infection with influenza viruses and for curing influenza (JP-A-6-22971).

[0063] The excellent activity of the compounds of the invention to inhibit the activated blood coagulation factor X was confirmed by the test methods mentioned below.

1) Method of measuring the time for blood coagulation with the human activated blood coagulation factor X:

[0064] The human activated blood coagulation factor X (Cosmo-Bio Co.) was dissolved in 0.05 M tris-HCl buffer (pH = 7.40) to prepare its solution of 0.05 units/ml. Blood was collected in 3.8 % sodium citrate to be 1/10 by volume, and centrifuged at 3,000 rpm for 10 minutes to separate human plasma therefrom. 90 µl of the thus-prepared human plasma, 10 µl of a test compound as diluted with physiological saline, and 50 µl of the solution of the activated blood coagulation factor X were kept warmed at 37°C for 3 minutes, to which was added 100 µl of a solution of 20 mM $CaCl_2$, and the time for blood coagulation in the system was measured.

[0065] To measure the coagulation time, used was Amelung's KC4A. The dose of the test compound for 2-time prolongation of the coagulation time (hereinafter referred to as CT2) was calculated on the basis of the coagulation time for the control to which was added 10 µl of physiological saline with no test compound. The results are shown in Table 1.

Table 1

Example No.	Test for measuring coagulation time with the human activated blood coagulation factor X, CT2 (µM)
17	0.092
22	0.111
23	0.110

Table 1 (continued)

Example No.	Test for measuring coagulation time with the human activated blood coagulation factor X, CT2 (μM)
24	0.152
32	0.089
33	0.098
36	0.069
72	0.119
73	0.224
75	0.095
84	0.134
Control compound	0.590
*) Control compound: A compound of Example 52 of JP-A-5-208946	

[0066] It has been verified that the compounds of the invention specifically inhibit the human activated blood coagulation factor X, and, while prolonging the coagulation time even at low concentrations, exhibit an excellent anticoagulation activity.

2) Method of measuring the coagulation time for mice in *exo vivo* (intravenous administration):

[0067] To test animals of male ICR mice (20 to 30 g, SLC Co.) that had been fed with nothing for 12 hours or longer, a solution of a test compound having been dissolved in physiological saline was intravenously administered only once through their tail vein. One minute after the administration, 0.6 ml of blood was collected from the animals which were anesthetized with diethyl ether, through their posterior artery in 3.8 % sodium citrate to be 1/10 by volume, and centrifuged at 3,000 rpm for 10 minutes to separate plasma therefrom. The extrinsic coagulation time (PT) and the intrinsic coagulation time (APTT) for this plasma were measured according to the following methods a) and b), respectively.

a) Extrinsic coagulation time (PT):

[0068] Tissue thromboplastin (54 mg/vial, freeze-dried powder by Ortho Co.) was dissolved in 2.5 ml of distilled water, and pre-warmed at 37°C. 50 μl of the plasma prepared in the above was kept warmed at 37°C for 1 minute, to which was added 50 μl of the thromboplastin solution, and the coagulation time was measured. To measure the coagulation time, used was Amelung's KC4A. The coagulation time for the control to which had been applied 50 μl of physiological saline with no test compound was also measured. Based on the value of the coagulation time for the control of being 1, obtained was the relative activity of the test compound.

b) Intrinsic coagulation time (APTT):

[0069] 50 μl of active thrombofacs (Ortho Co.) and 50 μl of the plasma prepared in the above were kept warmed at 37°C for 3 minutes, to which was added 50 μl of a solution of 20 mM $CaCl_2$ having been previously warmed at 37°C, and the coagulation time was measured. To measure the coagulation time, used was Amelung's KC4A. The coagulation time for the control to which had been administered physiological saline with no test compound was also measured. Based on the value of the coagulation time for the control of being 1, obtained was the relative activity of the test compound. The dose dependency of the anticoagulation activity of the compounds of the invention and also the time-dependent change in the activity thereof were also studied in the same manner as above, in which the dose and the time for blood collection were varied.

[0070] The data obtained in those experiments verified that the intravenous administration of the compounds of the invention well prolongs the coagulation time.

3) Method of measuring the coagulation time for mice in *exo vivo* (oral administration):

[0071] The same test animals as in 2) were further tested in the same manner as above, except that the solution of a test compound was orally administered in a forced manner through a gastric tube inserted thereinto, in place of the single intravenous administration in 2), and that blood was collected from each test animal in 30 minutes after the oral administration.

[0072] The test data obtained herein verified that the oral administration of the compounds of the invention well prolongs the coagulation time.

4) Method of measuring the coagulation time for crab-eating macaque in *exo vivo* (oral administration):

[0073] To test animals of male cynomolgus monkey (3 to 6 kg, Hamri Co.) that had been fed with nothing for 12 hours or longer, a solution or suspension of a test compound having been dissolved in physiological saline or suspended in a solution of 0.5 % methyl cellulose was orally administered in a forced manner through a gastric tube inserted thereinto. 3 ml of blood was collected from the thus-treated animals not being anesthetized, through their femoral vein at predetermined time intervals, in 3.8 % sodium citrate to be 1/10 by volume, and centrifuged at 3,000 rpm for 10 minutes to separate human plasma therefrom. The extrinsic coagulation time (PT) and the intrinsic coagulation time (APTT) for this plasma were measured according to the same methods as in 2).

[0074] The test data obtained herein verified that the oral administration of the compounds of the invention exhibits good bioavailability and has a superior function for prolonging the coagulation time.

[0075] Pharmaceutical compositions comprising, as the active ingredient, one or more of the compounds of formula (I) and their pharmaceutically acceptable salts of the invention can be formulated along with ordinary pharmaceutical carriers, vehicles and other additives into tablets, powders, fine granules, granules, capsules, pills, liquid preparations, injections, suppositories, ointments, cataplasms, and the like, and are administered orally or parenterally.

[0076] The clinical dose of the compounds of the invention may be suitably determined, depending on the conditions, the body weight, the age and the sex of the patients to which they are administered, but is, in general, from 0.1 to 500 mg/adult/day for oral administration, and from 0.01 to 100 mg/adult/day for parenteral administration. This may be administered to the patients all at a time, or may be divided into a few portions for administration in different times. Since the dose may vary depending on various conditions, a smaller dose than the defined range may well be employed, as the case may be.

[0077] As the solid composition for oral administration of the compounds of the invention, employed are tablets, powders, granules, etc. The solid composition of those types comprises one or more active substances along with at least one inert diluent, such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, meta-silicic acid, and magnesium aluminate. In an ordinary manner, the composition may contain any other additives except the inert diluents noted above, for example, a lubricant such as magnesium stearate, a disintegrator such as calcium cellulose glycolate, a stabilizer such as lactose, and a solubilizer or dissolution promoter such as glutamic acid or aspartic acid. If desired, the tablets and pills may be coated with a film of gastric or enteric substances such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, etc.

[0078] The liquid composition for oral administration includes, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, and the like, which contain ordinary inactive diluents such as purified water and ethyl alcohol. In addition to the inert diluents, those compositions may further contain pharmaceutical aids such as solubilizers, dissolution promoters, wetting promoters, suspension promoters, and also sweeteners, flavorings, aromas, and preservatives.

[0079] The injection for parenteral administration includes, for example, germ-free, aqueous or non-aqueous solutions, suspensions and emulsions. The diluent for the aqueous solutions and suspensions includes, for example, distilled water and physiological saline for injections. The diluent for the non-aqueous solutions and suspensions includes, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethyl alcohol, Polysolvate 80 (trade name), etc. Those compositions may further contain additives such as isotonicating promoters, preservatives, wetting promoters, emulsifiers, dispersants, stabilizers (e.g., lactose), solubilizers, dissolution promoters, etc. The compositions are sterilized by filtering them through bacteria-trapping filters, or by adding microbicides thereto, or by exposing them to radiations. The germ-free, solid compositions thus produced may be dissolved in germ-free water or in germ-free solvents for injection, before using them.

[0080] Where the compounds of the invention have low solubility, they may be processed for solubilization. For the solubilization treatment, employable are any known methods applicable to pharmaceutical preparations. For example, employed are a method of adding surfactants (e.g., polyoxyethylene-hardened castor oils, etc.) to the compounds; and a method of forming solid dispersions comprising the compounds and solubilizers (for example, water-soluble polymers, e.g., hydroxypropylmethyl cellulose, etc., and enteric polymers, e.g., carboxymethylethyl cellulose). If desired, further employed are a method of forming soluble salts, and a method of forming clathrate compounds with cyclodextrin

or the like. The solubilizing means may be suitably modified depending on the chemicals to be processed therewith ("Recent Pharmaceutical Techniques and Their Applications", in the *Journal of Medicines,* 157-159, 1983; and *Pharmacological Monograph No. 1,* "Bioavailability", published by Soft Science Co., 78-82, 1988). Of those, preferred is the method of forming solid dispersions of chemicals and solubilizers to improve the solubility of the chemicals (JP-A-56-49314; FR 2,460,667).

Best Mode for Carrying Out the Invention:

[0081] Now, the method for producing the compounds of the invention is described concretely hereunder, with reference to the following Examples of demonstrating the production of the compounds. It is to be construed that the compounds of the invention are not limited to those described in the following Examples but that the invention encompasses all of the compounds represented by the foregoing general formula (I) and their salts, hydrates, solvates, tautomers, optical isomers and polymorphic crystals. Some starting compounds for the compounds of the invention are novel, and the method for producing such novel compounds is demonstrated in the following Reference Examples.

Reference Example 1:

[0082] 1.8 g of 1-t-butoxycarbonylhexahydro-1H-1,4-diazepine was dissolved in 10 ml of DMF, to which were added 1.62 g of 4-fluoronitrobenzene and 1.84 g of potassium carbonate, and stirred at 90°C for 13 hours. After the reaction mixture was cooled, ethyl acetate was added thereto, and the mixture was washed with water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was dissolved in 10 ml of 1,4-dioxane, to which was added 4 ml of 4 N hydrochloric acid (in 1,4-dioxane), and stirred at 80°C for 16 hours. The reaction mixture was cooled, and then evaporated. 50 ml of diethyl ether was added to the resulting residue; and then filtered to obtain 2.11 g of 1-(4-nitrophenyl)hexahydro-1H-1,4-diazepine dihydrochloride.

Reference Example 2:

[0083] 2 g of the compound obtained in Reference Example 1 was dissolved in 20 ml of isoamyl alcohol, to which were added 1.02 g of 4-chloropyridine hydrochloride and 2.57 g of sodium hydrogencarbonate, and heated under reflux for 24 hours. Then, 500 mg of 4-chloropyridine hydrochloride was added to the reaction mixture, and further heated under reflux for 24 hours. The reaction mixture was cooled, and then evaporated. Chloroform was added to the resulting residue, which was then washed with water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was dissolved in 30 ml of 1,4-dioxane, to which were added 0.95 ml of triethylamine and 1.48 g of di-t-butyl dicarbonate, and stirred at room temperature for 12 hours. The reaction mixture was evaporated, and the resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (10/1) to obtain 1.94 mg of 1-(4-nitrophenyl)-4-(4-pyridyl)hexahydro-1H-1,4-diazepine.

Reference Example 3:

[0084] 100 mg of a 10 % palladium-carbon powder was suspended in 1 ml of methanol, to which was added a solution of 460 mg of the compound obtained in Reference Example 2 and dissolved in 20 ml of methanol, and stirred in a hydrogen atmosphere at room temperature for 8 hours. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The resulting residue was dissolved in 20 ml of 1,2-dichloroethane, to which were added 290 mg of 7-formyl-2-naphthalene-carbonitrile, 0.41 ml of acetic acid and 458 mg of sodium triacetoxyborohydride, and stirred at room temperature for 21 hours. Chloroform was added to the reaction mixture, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saturated saline in that order, then dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (10/1) to obtain 429 mg of 7-[[4-[4-(4-pyridyl)hexahydro-1H-1,4-diazepin-1-yl]anilino]methyl]-2-naphthalenecarbonitrile.

Reference Example 4:

[0085] 420 mg of the compound obtained in Reference Example 3 was dissolved in 10 ml of 1,2-dichloromethane, to which were added 0.2 ml of triethylamine and 0.11 ml of methanesulfonyl chloride, and stirred at room temperature for 12 hours. Chloroform was added to the reaction mixture, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (20/1) to obtain 340 mg of N-[(7-cyano-2-naphthyl)methyl]-N-[4-[4-(4-pyridyl)hexahydro-1H-1,4-

diazepin-1-yl]phenyl]methanesulfonamide.

[0086] In the same manner as in Reference Example 4, obtained were compounds of Reference Examples 5 and 6 shown in Table 10.

Reference Example 7:

[0087] 3.0 g of 4-fluoro-3-methylnitrobenzene was dissolved in 20 ml of DMF, to which were added 5.81 g of hexahydro-1H-1,4-diazepine and 3.94 g of potassium carbonate, and stirred at 90°C for 4 hours.

[0088] After the reaction mixture was cooled, chloroform was added thereto, and the mixture was washed with water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (5/1) to obtain 3.78 g of 1-(2-methyl-4-nitrophenyl)hexahydro-1H-1,4-diazepine.

[0089] In the same manner as in Reference Example 7, obtained were compounds of Reference Examples 8 to 10 shown in Table 7.

Reference Example 11:

[0090] 5.8 g of 5-(hexahydro-1H-1,4-diazepin-1-yl)-2-nitrobenzonitrile obtained in Reference Example 10 was dissolved in 20 ml of ethanol, to which was added aqueous 6 M sodium hydroxide, and heated under reflux for 15 hours. The reaction mixture was cooled, neutralized with concentrated hydrochloric acid, and then evaporated. The resulting residue was dissolved in 150 ml of methanol, to which was added 10 ml of sulfuric acid, and then heated under reflux for 2 days. The reaction mixture was cooled, and then evaporated. The resulting residue was dissolved in a small amount of water, and then neutralized with sodium carbonate. Chloroform was added to this, which was then washed with saturated saline, dried over anhydrous sodium sulfate, and then evaporated to obtain 4.21 g of methyl 5-(hexahydro-1H-1,4-diazepin-1-yl)-2-nitrobenzoate.

Reference Example 12:

[0091] 21.4 g of hexahydro-1H-1,4-diazepine was dissolved in 214 ml of DMF, to which were added 10.1 g of 4-fluoronitrobenzene and 19.7 g of potassium carbonate, and stirred at 90°C for 7 hours. The reaction mixture was evaporated, and chloroform was added to the resulting residue, which was then washed with aqueous 10 % potassium hydrogencarbonate and saturated saline in that order, dried over anhydrous magnesium sulfate, and then evaporated to remove the solvent. The resulting residue was dissolved in 210 ml of 1,2-dichloroethane, to which were added 86.5 g of triethylamine and 93.4 g of di-t-butyl dicarbonate, and stirred at room temperature for 13 hours. The reaction mixture was washed with water, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was washed with diethyl ether to obtain 14.12 g of 4-t-butoxycarbonyl-1-(4-nitrophenyl)hexahydro-1H-1,4- diazepine.

[0092] In the same manner as in Reference Example 12, obtained were compounds of Reference Examples 13 and 14 shown in Table 8.

Reference Example 15:

[0093] 3.7 g of the compound obtained in Reference Example 7 was dissolved in 50 ml of 1,4-dioxane, to which were added 3.23 ml of triethylamine and 5.2 g of di-t-butyl dicarbonate, and stirred at room temperature for 90 minutes. The reaction mixture was evaporated, and chloroform was added to the resulting residue. This was washed with water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (50/1) to obtain 7.64 g of 4-t-butoxycarbonyl-1-(2-methyl-4-nitrophenyl)hexahydro-1H- 1,4-diazepine.

[0094] In the same manner as in Reference Example 15, obtained were compounds of Reference Examples 16 to 18 shown in Table 8.

Reference Example 19:

[0095] 14.12 g of 4-t-butoxycarbonyl-1-(4-nitrophenyl)hexahydro-1H-1,4-diazepine obtained in Reference Example 12 was suspended in 44 ml of ethanol, to which was added 700 mg of 10 % palladium-carbon, and stirred in a hydrogen atmosphere at room temperature for 16 hours. The reaction mixture was filtered, and then evaporated. The resulting residue was dissolved in 440 ml of 1,2-dichloroethane, to which were added 7.95 g of 7-formyl-2-naphthalenecarbonitrile, 26 ml of acetic acid and 18.5 g of sodium triacetoxyborohydride in that order, and stirred at room temperature for 2 hours.

[0096] 0.8 g of 7-formyl-2-naphthalenecarbonitrile and 1.9 g of sodium triacetoxyborohydride were added to this, and further stirred for 1 hour. 0.8 g of 7-formyl-2-naphthalenecarbonitrile and 1.9 g of sodium triacetoxyborohydride were further added to this, and still further stirred for 2 hours. The reaction mixture was washed with aqueous 10 % potassium carbonate and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue weighed 25.01 g. 7.04 g of this was purified through silica gel column chromatography using an eluent solvent of hexane/ethyl acetate (3/1) to obtain 4.45 g of 7-[[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)anilino]methyl]-2-naphthalenecarbonitrile.

Reference Example 20:

[0097] 2.1 g of the compound obtained in Reference Example 15 was dissolved in 10 ml of methanol, to which were added 300 mg of 10 % palladium-carbon and 2.1 g of ammonium formate, and stirred at room temperature for 5 hours.

[0098] The reaction mixture was filtered through Celite, and the filtrate was evaporated. Chloroform was added to the resulting residue, which was then washed with water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was dissolved in 20 ml of 1,2-dichlroethane, to which were added 835 mg of 7-formyl-2-naphthalenecarbonitrile, 1.28 ml of acetic acid and 1.5 g of sodium triacetoxyborohydride in that order, and stirred at room temperature for 14 hours. Chloroform was added to the reaction mixture, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (30/1) to obtain 1.94 g of 7-[[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)-3- methylanilino]methyl]-2-naphthalenecarbonitrile.

Reference Example 21-1:

[0099] 2.1 g of 1-t-butoxycarbonyl-4-(2-chloro-4-nitrophenyl)hexahydro-1H-1,4-diazepine obtained in Reference Example 16 was dissolved in 10 ml of a 4 N hydrochloric acid-1,4-dioxane solution, and stirred at 80°C for 2 hours. The reaction mixture was evaporated. Chloroform was added to the resulting residue, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated.

[0100] The resulting residue was dissolved in 20 ml of 1,2-dichloroethane, to which were added 0.6 ml of benzaldehyde, 1.65 ml of acetic acid and 1.9 g of sodium triacetoxyborohydride, and stirred at room temperature for 17 hours. Chloroform was added to the reaction mixture, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saline in that order, dried over anhydrous sodium sulfate, and then evaporated.

[0101] The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (40/1) to obtain 1.47 g of 4-benzyl-1-(2-chloro-4-nitrophenyl)hexahydro-1H-1,4-diazepine.

Reference Example 21-2:

[0102] 1.4 g of the compound obtained in Reference Example 21-1 was dissolved in 20 ml of ethanol and 20 ml of water, to which were added 2.26 g of reduced iron and 108 mg of ammonium chloride, and heated under reflux for 3 hours. The reaction mixture was cooled, filtered through Celite, and then evaporated.

[0103] Chloroform was added to the resulting residue, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was dissolved in 20 ml of 1,2-dichloroethane, to which were added 684 mg of 7-formyl-2-naphthalenecarbonitrile, 1.05 ml of acetic acid and 1.24 g of sodium triacetoxyborohydride, and stirred at room temperature for 24 hours.

[0104] Chloroform was added to the reaction mixture, which was then washed with aqueous saturated sodium hydrogencarbonate, water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (50/1) to obtain 1.61 g of 7-[[4-(4-benzylhexahydro-1H-1,4-diazepin-1-yl)-3-chloro anilino]methyl]-2-naphthalenecarbonitrile.

Reference Example 21-3:

[0105] 642 mg of the compound obtained in Reference Example 21-2 was dissolved in 20 ml of 1,2-dichloroethane, to which was added 1.44 ml of 1-chloroethyl chloroformate, and stirred at 90°C for 16 hours. The reaction mixture was cooled, and then evaporated. The resulting residue was dissolved in 20 ml of methanol, and heated under reflux for 2 hours. The reaction mixture was cooled, and then evaporated. The resulting residue was dissolved in 20 ml of 1,4-diox-

ane, to which were added 270 mg of di-t-butyl dicarbonate and 0.21 ml of triethylamine, and stirred at room temperature for 7 hours.

[0106] The reaction mixture was evaporated, and the resulting residue was purified through silica gel column chromatography using an eluent solvent of hexane/ethyl acetate (4/1) to obtain 298 mg of 7-[[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)-3-chloroanilino]methyl]-2-naphthalenecarbonitrile. In the same manner as in Reference Example 19, obtained were compounds of Reference Examples 22 and 23 shown in Table 9.

Reference Example 24:

[0107] 400 mg of 7-[[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)anilino]methyl]-2-naphthalenecarbonitrile obtained in Reference Example 19 was dissolved in 5 ml of 1,2-dichloroethane, and stirred at 3°C. 208 mg of pyridine and 201 mg of methanesulfonyl chloride were added to this, and stirred at room temperature for 12 hours. Chloroform was added to the reaction mixture, which was then washed with aqueous saturated sodium hydrogencarbonate, water, aqueous 10 % citric acid and water in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was recrystallized from methanol to obtain 342 mg of N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl)methanesulfonamide.

[0108] In the same manner as in Reference Example 24, obtained were compounds of Reference Examples 25 to 35 and Reference Example 40 shown in Table 10.

Reference Example 36:

[0109] 509 mg of the compound obtained in Reference Example 19 was dissolved in 5 ml of 1,2-dichloroethane, to which was added 401 mg of ethoxycarbonyl isocyanate, and stirred at room temperature for 3 hours. Aqueous 10 % citric acid was added to the reaction mixture, which was then extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of ethanol/chloroform (2/98) to obtain 637 mg of ethyl N-[N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]carbamoyl]carbamate.

Reference Example 37:

[0110] 1.62 g of 4-t-butoxycarbonyl-1-(2-fluoro-4-nitrophenyl)hexahydro-1H-1,4-diazepine obtained in Reference Example 13 was suspended in 48 ml of ethanol, to which was added 160 mg of 10 % palladium-carbon, and stirred in a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered, and then evaporated. The resulting residue weighed 1.62 g. 0.61 g of this was dissolved in 20 ml of 1,2-dichloroethane, to which were added 357 mg of 7-formyl-2-naphthalenecarbonitrile, 1.2 g of acetic acid and 823 mg of sodium triacetoxyborohydride in that order, and stirred at room temperature for 2 hours. The reaction mixture was washed with aqueous 10 % sodium carbonate and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was dissolved in 20 ml of 1,2-dichloroethane, to which were added 467 mg of pyridine and 560 mg of ethyl chlorosulfonylacetate at 0°C, and stirred for 1 hour. One ml of ethanol was added to this, and stirred for 1 hours, and then, the reaction mixture was concentrated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of hexane/ethyl acetate (3/1) to obtain 1.08 g of ethyl [N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)-3-fluorophenyl]-N-[(7-cyano-2-naphthyl)methyl]sulfamoyl]acetate.

[0111] In the same manner as in Reference Example 37, obtained was a compound of Reference Example 38 shown in Table 10.

Reference Example 39:

[0112] 1.7 g of t-butyl N-[N-(4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]sulfamoyl]carbamate obtained in Reference Example 27 was dissolved in 20 ml of DMF, to which were added 0.44 ml of ethyl bromoacetate and 543 mg of potassium carbonate, and stirred at room temperature for 24 hours. Chloroform was added to the reaction mixture, which was then washed with water and saturated saline in that order, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of chloroform/methanol (30/1) to obtain 1.68 g of ethyl N-[N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1- yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]sulfamoyl]-N-t-butoxycarbonylglycinate.

Example 1:

[0113] 330 mg of N-[(7-cyano-2-naphthyl)methyl]-N-[4-[4-(4-pyridyl)hexahydro-1H-1,4-diazepin-1-yl]phenyl]meth-

anesulfonamide obtained in Reference Example 4 was dissolved in a mixture of 2 ml of chloroform and 10 ml of ethanol. The resulting solution was cooled to -20°C with stirring, into which was introduced hydrogen chloride up to saturation. The reaction mixture was stirred at 5°C for 17 hours, and then evaporated. The resulting residue was dissolved in 10 ml of ethanol, to which was added 247 mg of ammonium acetate, and stirred at room temperature for 24 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS (YMC-GEL ODS-A 120-230/70, hereinafter the same) column chromatography using an eluent solvent of methanol/water (2/98). A small amount of 1 N hydrochloric acid was added to the purified product, which was further evaporated to obtain 64 mg of N-[(7-amidino-2-naphthyl)methyl]-N-[4-[4-(4-pyridyl)hexahydro- 1H-1,4-diazepin-1-yl]phenyl]methanesulfonamide dihydrochloride.

[0114] In the same manner as in Example 1, obtained were compounds of Examples 2 and 3 shown in Table 2.

Example 4:

[0115] 340 mg of ethyl [N-[(7-amidino-2-naphthyl)methyl]-N-[4-[4-(4-pyridyl)hexahydro-1H-1,4-diazepin-1-yl]phenyl]sulfamoyl]acetate dihydrochloride obtained in Example 2 was dissolved in a mixture of 10 ml of 1,4-dioxane and 10 ml of water, to which was added 3 ml of aqueous 1 N sodium hydroxide, and stirred at room temperature for 3 hours. 3 ml of 1 N hydrochloric acid was added to the reaction mixture, and then evaporated. The resulting residue was purified through ODS column chromatography using an eluent solvent of acetonitrile/water (10/90), and a small amount of 1 N hydrochloric acid was added to the purified product, which was then freeze-dried to obtain 154 mg of [N-[(7-amidino-2-naphthyl)methyl]-N-[4-[4-(4-pyridyl)hexahydro- 1H-1,4-diazepin-1-yl]phenyl]sulfamoyl]acetic acid dihydrochloride.

[0116] In the same manner as in Example 4, obtained were a compound of Example 5 shown in Table 2, a compound of Example 85 shown in Table 4 and compounds of Examples 90 to 93 shown in Table 7, respectively.

Example 6:

[0117] 5.19 g of ethyl [N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]sulfamoyl]acetate obtained in Reference Example 26 was dissolved in a mixture of 9 ml of chloroform and 9 ml of ethanol. The resulting solution was cooled at -20°C with stirring, into which was introduced hydrogen chloride up to saturation. The reaction mixture was stirred at 5°C for 23 hours, and then evaporated. The resulting residue was dissolved in 18 ml of ethanol, to which was added 6.6 g of ammonium acetate, and stirred at room temperature for 28 hours. The resulting reaction mixture was evaporated, and the residue thus obtained was purified through ODS column chromatography using an eluent solvent of ethanol/water (10/90). A small amount of 1 N hydrochloric acid was added to this, which was then freeze-dried to obtain 1.02 g of ethyl [N-[(7-amidino-2-naphthyl)methyl]-N-[4-(hexahydro-1H-1,4-diazepin-1-yl)phenyl]sulfamoyl]acetate dihydrochloride.

[0118] In the same manner as in Example 6, obtained were compounds of Examples 7 to 15 shown in Table 2, compounds of Examples 45 to 63 shown in Table 3 and a compound of Example 86 shown in Table 5, respectively.

Example 16:

[0119] 333 mg of N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]methanesulfonamide obtained in Reference Example 24 was dissolved in 10 ml of ethanol, and the resulting solution was cooled to -20°C with stirring, into which was introduced hydrogen chloride up to saturation. The reaction mixture was stirred at 5°C for 15 hours, and then evaporated. The resulting residue was dissolved in a mixture of 10 ml of ethanol and 10 ml of methanol, to which was added 480 mg of ammonium acetate, and stirred at room temperature for 24 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography. From the fraction having been eluted with an eluent solvent of methanol/water (5/95), obtained was 249 mg of a roughly-purified product of N-[(7-amidino-2-naphthyl)methyl]-N-[4-(hexahydro-1H-1,4-diazepin-1-yl)phenyl]sulfonamide. 224 mg of this product was dissolved in 10 ml of ethanol, to which were added 650 mg of ethyl acetimidate hydrochloride and 683 mg of triethylamine, and stirred at room temperature for 20 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS (YMC-GEL ODS-A 120-230/70) column chromatography using an eluent solvent of methanol/water (5/95). A small amount of 1 N hydrochloric acid was added to the thus-purified product, which was then freeze-dried to obtain 169 mg of N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]methanesulfonamide dihydrochloride.

[0120] In the same manner as in Example 16, obtained were compounds of Examples 17 to 21 shown in Table 2 and compounds of Examples 64 and 65 shown in Table 3, respectively.

Example 22:

[0121] 590 mg of ethyl [N-[(7-amidino-2-naphthyl)methyl]-N-[4-(hexahydro-1H-1,4-diazepin-1-yl)phenyl]sulfa-

moyl]acetate dihydrochloride obtained in Example 6 was dissolved in 22 ml of ethanol, to which were added 680 mg of ethyl acetimidate hydrochloride and 555 mg of triethylamine, and stirred at room temperature for 15 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of ethanol/water (10/90). A small amount of 1 N hydrochloric acid was added to this, which was then freeze-dried to obtain 118 mg of ethyl [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetate dihydrochloride.

[0122] In the same manner as in Example 22, obtained were compounds of Examples 23 to 29 shown in Table 2, compounds 66 to 70 shown in Table 3, compounds of compounds of Examples 71 to 73 shown in Table 4, a compound of Example 87 shown in Table 5 and a compound of Example 89 shown in Table 6, respectively.

Example 30:

[0123] 1.37 g of methyl N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]malonamate obtained in Reference Example 29 was dissolved in a mixture of 15 ml of chloroform and 15 ml of methanol, and the resulting solution was cooled to -20°C with stirring, into which was introduced hydrogen chloride up to saturation. The reaction mixture was stirred at 5°C for 21 hours, and then evaporated. The resulting residue was dissolved in 30 ml of methanol, to which was added 2.3 g of ammonium acetate, and stirred at room temperature for 3 days. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of methanol/water (5/95) to obtain a roughly-purified product of methyl N-[(7-amidino-2-naphthyl)methyl]-N-[4-(hexahydro-1H-1,4-diazepin-1-yl)phenyl]malonamate.

[0124] This product was dissolved in 30 ml of methanol, to which were added 5.56 g of ethyl acetimidate hydrochloride and 4.45 g of triethylamine, and stirred at room temperature for 2 days. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of methanol/water (5/95). A small amount of 1 N hydrochloric acid was added to the thus-purified product, which was then freeze-dried to obtain 950 mg of methyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]malonamate dihydrochloride.

Example 31:

[0125] 980 mg of ethyl [N-[(7-amidino-2-naphthyl)methyl]-N-[4-(hexahydro-1H-1,4-diazepin-1-yl)-3-fluorophenyl]sulfamoyl]acetate dihydrochloride obtained in Example 11 was dissolved in 36 ml of ethanol, to which were added 1.12 g of ethyl acetimidate hydrochloride and 920 mg of triethylamine, and stirred at room temperature for 5 days. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of ethanol/water (10/90) to obtain a roughly-purified product of ethyl [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-fluorophenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetate. 1.02 g of this product was dissolved in 21 ml of concentrated hydrochloric acid, and stirred at room temperature for 16 hours. The reaction mixture was evaporated, and the resulting residue was dissolved in 20 ml of concentrated hydrochloric acid, and stirred at room temperature for 4 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of acetonitrile/water (5/95), and a small amount of 1 N hydrochloric acid was added to the thus-purified product, which was then freeze-dried to obtain 940 mg of [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-fluorophenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamo yl]acetic acid dihydrochloride.

[0126] In the same manner as in Example 31, obtained was a compound of Example 32 shown in Table 2.

Example 33:

[0127] 450 mg of ethyl [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetate dihydrochloride obtained in Example 22 was dissolved in 8 ml of concentrated hydrochloric acid, and stirred at room temperature for 14 hours. The reaction mixture was evaporated, and the resulting residue was dissolved in 8 ml of concentrated hydrochloric acid, and stirred at room temperature for 4 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of acetonitrile/water (10/90). A small amount of 1 N hydrochloric acid was added to this, which was then freeze-dried to obtain 302 mg of [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetic acid dihydrochloride.

[0128] In the same manner as in Example 33, compounds of Examples 34 and 35 shown in Table 2, compounds of Examples 36 to 42 shown in Table 3 and compounds of Examples 74 to 84 shown in Table 4, respectively.

Example 43:

[0129] 300 mg of [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-fluorophenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetic acid dihydrochloride obtained in Example 31 was dissolved in 10 ml of ethanol, to which was added 1 ml of a 4 N hydrochloric acid gas-dioxane solution, and stirred at room temperature for 22 hours. The reaction mixture was evaporated, and the resulting residue was dissolved in 20 ml of ethanol, to which was added 2 ml of a 4 N hydrochloric acid gas-dioxane solution, and stirred at room temperature for 7 hours. The reaction mixture was evaporated, and the resulting residue was purified through ODS column chromatography using an eluent solvent of ethanol. A small amount of 1 N hydrochloric acid was added to the thus-purified product, which was then freeze-dried to obtain 238 mg of ethyl [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-fluorophenyl]-N-[(7-amidino-2- naphthyl)methyl]sulfamoyl]acetate dihydrochloride.

[0130] In the same manner as in Example 43, obtained was a compound of Example 44 shown Table 3.

Example 88:

[0131] 538 mg of the compound obtained in Reference Example 40 was dissolved in a mixture of 10 ml of pyridine and 2 ml of triethylamine, into which was introduced a hydrogen sulfide gas at 0°C with stirring up to saturation. The reaction mixture was stirred at room temperature for 14 hours, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of ethyl acetate/chloroform (1/2) to obtain 436 mg of N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N- [(5-thiocarbamoyl-2-benzofuranyl)methyl]methanesulfonamide. 436 mg of this compound was dissolved in 9 ml of acetone, to which was added 0.6 ml of methyl iodide. The mixture was stirred for 1.5 hours under heating for reflux. The solvent was evaporated, and the residue was dissolved in 8 ml of methanol, to which was added 267 mg of ammonium acetate. The mixture was stirred for one hour under heating for reflux. The solvent was evaporated, and the resulting residue was purified through silica gel column chromatography using an eluent solvent of methanol/chloroform (1/9). 412 mg of a roughly-purified product of N-[4-(4-t-butoxycarbonylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(5-amidino-2-benzofuranyl)methyl]methanesulfonamide was dissolved in 16 ml of 1,4-dioxane, to which was added 8 ml of a 4 N hydrogen chloride-1,4-dioxane solution. The reaction mixture was stirred at room temperature for 40 minutes, and the solvent was evaporated. The resulting residue was purified through ODS column chromatography using an eluent solvent of methanol/water (5/95), and a small amount of 1 N hydrochloric acid was added to the thus-purified product, which was then freeze-dried to obtain 108 mg of N-[(5-amidino-2-benzofuranyl)methyl]-N-(4-(1H-1,4-diazepin-1-yl)phenyl]methanesulfonamide trihydrochloride.

Example 94:

[0132] 230 mg of N-[4-(4-methylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-cyano-2-naphthyl)methyl]sulfamide was dissolved in 9.2 ml of ethanol, to which were added 0.25 ml of triethylamine and 90 mg of hydroxylamine hydrochloride. The mixture was heated for reflux for 2 hours. The reaction mixture was evaporated, and the resulting residue was purified through silica gel column chromatography using an eluent solvent of concentrated ammonia water/methanol/chloroform (0.1/1/7). The solvent was evaporated, and a small amount of aqueous 1 N hydrochloric acid was to the residue, and then evaporated again in vacuo, to obtain 41 mg of N-[(7-hydroxyamidino-2-naphthyl)methyl]-N-[4-(4-methylhexahydro-1H-1,4-diazepin-1-yl)phenyl]sulfamide trichloride.

[0133] In the same manner as in Example 94, obtained were compounds of Examples 95 to 101 shown Table 7.

Example 102:

[0134] 210 mg of {N-[(7-amidino-2-naphthyl)methyl]-N-[4-(4-methylhexahydro-1H-1,4-diazepin-1-yl)phenyl]}sulfamide was dissolved in 4 ml of dimethyl sulfoxide, to which were added 0.23 ml of triethylamine and 0.042 ml of methyl chloroformate. The mixture was stirred at room temperature for 50 minutes. To the reaction mixture was added aqueous saturated sodium hydrogencarbonate. The mixture was extracted with chloroform, dried over anhydrous sodium sulfate, and then evaporated. The resulting residue was purified through silica gel column chromatography using an eluent solvent of concentrated ammonia water/methanol/chloroform (0.1/1/10). The solvent was evaporated, and a small amount of aqueous dilute hydrochloric acid was added to the residue, which was then freeze-dried to obtain 121 mg of N-{[7-(N-methoxycarbonylamidino)-2-naphthyl]methyl}-N-[4-(4- methylhexahydro-1H-1,4-diazepin-1-yl)phenyl]sulfamide trihydrochloride.

[0135] In the same manner as in Example 102, obtained were compounds of Examples 103 to 107 shown Table 7.

[0136] The structural formulae and the physico-chemical data of the compounds of the Reference Examples are shown in Tables 8 to 14; the structural formulae of the compounds of the Examples are shown in Tables 2 to 7; and the physico-chemical data of the compounds of the Examples are shown in Tables 15 to 24. Further, the compounds having

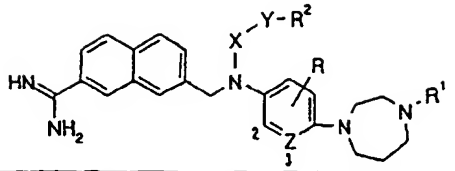
the structural formulae shown in Tables 25 to 27 can be produced in substantially the same manners described in the foregoing Examples or Production Examples, or can be easily produced by applying thereto small modifications which are obvious to those skilled in the art.

[0137] The meanings of the symbols in those Tables are mentioned below.

Rf: Reference Example No.
Ex: Example No.
NMR: Nuclear magnetic resonance spectrum
MS: Mass analytical data
Me: Methyl
Et: Ethyl
Py: Pyridyl
Bn: Benzyl
nBu: n-Butyl
iPr: Isopropyl
Boc: Butoxycarbonyl group
Tet: Tetrazolyl group

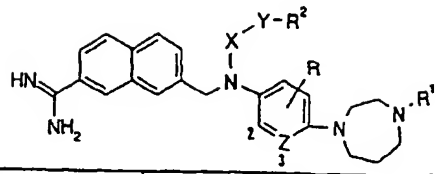
[0138] "2-" and "3-" that precede the substituents in those Tables mean, irrespective of the chemical names of the substituents, that the indicated substituents are bonded to the "2" and "3" positions, respectively, of the structural formulae in the Tables.

Table 2



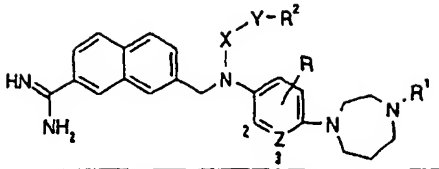
Ex	R^1	X	Y	R^2	Z	R	Sal
1	4-py	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
2	4-py	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
3	4-py	-CO-	$-CH_2CH_2-$	-COOMe	CH	H	2HCl
4	4-py	$-SO_2-$	$-CH_2-$	-COOH	N	H	2HCl
5	4-py	-CO-	$-CH_2-$	-COOH	CH	H	2HCl
6	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
7	H	$-SO_2NH-$	$-CH_2-$	-COOEt	CH	H	2HCl
8	H	-CO-	$-CH_2-$	-COOEt	CH	H	2HCl
9	H	-CO-	$-CH_2CH_2-$	-COOEt	CH	H	2HCl
10	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Me	2HCl
11	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-F	2HCl
12	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Cl	2HCl
13	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-Me	2HCl
14	H	$-SO_2-$	$-CH_2-$	-COOMe	CH	2-COOMe	2HCl
15	H	$-SO_2-$	$-CH_2-$	-COOEt	N	H	2HCl
16	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
17	-C(=NH)-Me	-CO-	$-CH_2-$	H	CH	H	2HCl
18	-C(=NH)-Me	$-SO_2NH-$	—	H	CH	H	2HCl
19	-C(=NH)-Me	$-SO_2NH-$	—	-COOEt	CH	H	2HCl
20	-C(=NH)-Me	-CONH-	$-CH_2-$	-COOEt	CH	H	2HCl
21	-C(=NH)-Me	-CONH-	—	-COOEt	CH	H	2HCl
22	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
23	-C(=NH)-Me	$-SO_2NH-$	$-CH_2-$	-COOEt	CH	H	2HCl
24	-C(=NH)-Me	-CO-	$-CH_2-$	-COOEt	CH	H	2HCl
25	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOEt	CH	H	2HCl
26	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	3-Me	2HCl
27	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Cl	2HCl
28	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-Me	2HCl
29	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOMe	CH	2-COOMe	2HCl
30	-C(=NH)-Me	-CO-	$-CH_2-$	-COOMe	CH	H	2HCl
31	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-F	2HCl
32	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	N	H	2HCl
33	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
34	-C(=NH)-Me	$-SO_2NH-$	$-CH_2-$	-COOH	CH	H	2HCl
35	-C(=NH)-Me	-CO-	$-CH_2-$	-COOH	CH	H	2HCl

Table 3



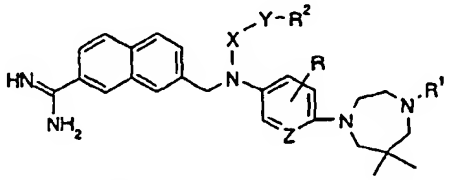
Ex	R^1	X	Y	R^2	Z	R	Sal
36	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOH	CH	H	2HCl
37	-C(=NH)-Me	-CONH-	$-CH_2-$	-COOH	CH	H	2HCl
38	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Me	2HCl
39	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	2-Me	2HCl
40	H	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
41	H	-CO-	$-CH_2-$	-COOH	CH	H	2HCl
42	H	-CO-	$-CH_2CH_2-$	-COOH	CH	H	2HCl
43	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	3-F	2HCl
44	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	-COOEt	N	H	2HCl
45	H	-CO-	$-CH_2-$	$-CONH_2$	CH	H	2HCl
46	H	-CO-	$-CH_2-$	-CONHMe	CH	H	2HCl
47	H	-CO-	$-CH_2-$	$-CON(Me)_2$	CH	H	2HCl
48	H	-CO-	—	-OEt	CH	H	2HCl
49	H	-CSNH-	$-CH_2-$	-COOEt	CH	H	2HCl
50	H	-CO-	$-CH_2-$	-Tet	CH	H	2HCl
51	-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
52	-Me	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
53	-Me	$-SO_2NH-$	—	-COOEt	CH	H	2HCl
54	-Me	$-SO_2NH-$	—	H	CH	H	2HCl
55	-Me	$-SO_2NH-$	$-CH_2-$	H	CH	H	2HCl
56	-Me	$-SO_2N(Me)-$	$-CH_2-$	H	CH	H	2HCl
57	-nBu	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
58	-Bn	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
59	$-C(=NH)-NH_2$	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	2HCl
60	$-CH_2COOEt$	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
61	$-CH_2CONH_2$	$-SO_2-$	$-CH_2-$	H	CH	H	2HCl
62	H	-CO-	$-CH_2-$	-COOEt	N	H	2HCl
63	H	-CO-	$-CH_2CH_2-$	-COOEt	N	H	2HCl
64	-C(=NH)-Me	-CO-	$-CH_2-$	-COOnBu	CH	H	2HCl
65	-C(=NH)-Me	-CO-	$-CH_2-$	-COOiPr	CH	H	2HCl
66	-C(=NH)-Me	-CO-	$-CH_2-$	$-CONH_2$	CH	H	2HCl
67	-C(=NH)-Me	-CO-	$-CH_2-$	-CONHMe	CH	H	2HCl
68	-C(=NH)-Me	-CO-	$-CH_2-$	$-CON(Me)_2$	CH	H	2HCl
69	-C(=NH)-Me	-CO-	—	-OEt	CH	H	2HCl
70	-C(=NH)-Me	-CSNH-	$-CH_2-$	-COOEt	CH	H	2HCl

Table 4



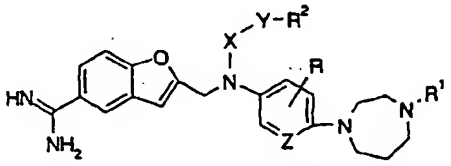
Ex	R^1	X	Y	R^2	Z	R	Sal
71	-C(=NH)-Me	-CO-	$-CH_2-$	-Tet	CH	H	2HCl
72	-C(=NH)-Me	-CO-	$-CH_2-$	-COOEt	N	H	2HCl
73	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOEt	N	H	2HCl
74	H	-CSNH-	$-CH_2-$	-COOH	CH	H	2HCl
75	-C(=NH)-Me	-CSNH-	$-CH_2-$	-COOH	CH	H	2HCl
76	-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
77	-nBu	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
78	-Bn	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
79	$-C(=NH)-NH_2$	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl
80	H	$-SO_2-$	$-CH_2-$	-COOH	N	H	2HCl
81	H	-CO-	$-CH_2-$	-COOH	N	H	2HCl
82	-C(=NH)-Me	-CO-	$-CH_2-$	-COOH	N	H	2HCl
83	H	-CO-	$-CH_2CH_2-$	-COOH	N	H	2HCl
84	-C(=NH)-Me	-CO-	$-CH_2CH_2-$	-COOH	N	H	2HCl
85	$-CH_2COOH$	$-SO_2-$	$-CH_2-$	-COOH	CH	H	2HCl

Table 5



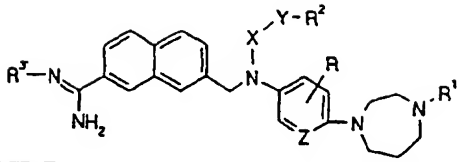
Ex.	R^1	X	Y	R^2	Z	R	Sal
86	H	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
87	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl

Table 6



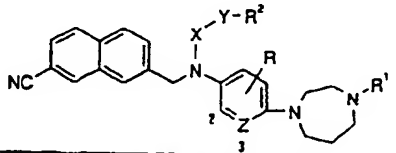
Ex.	R^1	X	Y	R^2	Z	R	Sal
88	H	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
89	-C(=NH)-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl

Table 7



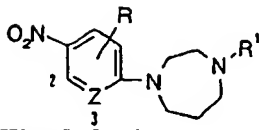
Ex.	$R^{3'}$	R^1	X	Y	R^2	Z	R	Sal
90	-OH	4-Py	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
91	-OH	-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
92	-COOMe	-Me	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
93	-OH	H	$-SO_2-$	$-CH_2-$	-COOH	CH	H	3HCl
94	-OH	-Me	$-SO_2NH-$	—	H	CH	H	3HCl
95	-OH	4-Py	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
96	-OH	-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
97	-OH	H	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
98	-OH	-Me	$-SO_2NH-$	$-CH_2-$	H	CH	H	3HCl
99	-OH	-Me	$-SO_2N(Me)-$	$-CH_2-$	H	CH	H	3HCl
100	-OH	-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
101	-OH	-Me	$-SO_2NH-$	—	-COOEt	CH	H	3HCl
102	-COOMe	-Me	$-SO_2NH-$	—	H	CH	H	3HCl
103	-COOMe	-Me	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	3HCl
104	-COOMe	-Me	$-SO_2NH-$	$-CH_2-$	H	CH	H	3HCl
105	-COOMe	-Me	$-SO_2N(Me)-$	$-CH_2-$	H	CH	H	3HCl
106	-COOMe	-Me	$-SO_2-$	$-CH_2-$	H	CH	H	3HCl
107	-COOMe	-Me	$-SO_2NH-$	—	-COOEt	CH	H	3HCl

Table 8



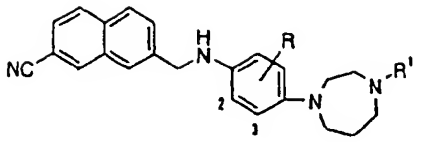
Rf	R^1	X	Y	R^2	Z	R	Rf.	R^1	X	Y	R^2	Z	R
4	3-py	$-SO_2-$	$-CH_2-$	H	CH	H	24	-Boc	$-SO_2-$	—	Me	CH	H
5	3-py	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	25	-Boc	-CO-	—	Me	CH	H
6	3-py	-CO-	$-CH_2-$	-COOMe	CH	H	27	-Boc	$-SO_2NH-$	—	-Boc	CH	H
26	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	H	28	-Boc	$-SO_2NH-$	—	-COOEt	CH	H
29	-Boc	-CO-	$-CH_2-$	-COOMe	CH	H	30	-Boc	-CONH-	$-(CH_2)_2-$	-COOEt	CH	H
32	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Me	31	-Boc	-CONH-	$-CH_2-$	-COOEt	CH	H
33	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-Cl	36	-Boc	-CONH-	—	-COOEt	CH	H
34	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-Me	38	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	N	H
35	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	2-COOMe	39	-Boc	$-SO_2N$(Boc)-	$-CH_2-$	-COOEt	H	H
37	-Boc	$-SO_2-$	$-CH_2-$	-COOEt	CH	3-F							

Table 9



Rf.	R^1	Z	R^3	DATA
1	H	CH	H	NMR(DMSO-d6) δ :2.07-2.18(2H,m),3.18-3.29(4H,m),3.67(2H,t, J=5.9Hz),3.90(2H,t,J=5.9Hz),6.92(2H,d,J=9.5Hz),8.09(2H,d,J=9 .5Hz),9.32(3H,br)
2	3-Py	CH	H	NMR($CDCl_3$) δ :2.02-2.21(2H,m),3.42-3.70(8H,m),6.55(2H,d,J=3.2 Hz),6.69(2H,d,J=9.5Hz),8.14(2H,d,J=9.5Hz),8.26(2H,d,J=3.2Hz)
7	H	CH	3-Me	NMR($CDCl_3$) δ :1.89-1.97(2H,m),2.38(3H,s),2.82-3.08(4H,m),3.35-3.73(4H,m),6.99(1H,d,J=8.9Hz),7.97-8.00(1H,m),8.61(1H,br)
8	H	CH	3-Cl	NMR($CDCl_3$) δ :1.93-2.03(2H,m),3.03(2H,t,J=5.8Hz),3.03(2H,t,J= 5.8Hz),3.53-3.61(4H,m),7.01(1H,d,J=9.1Hz),8.01(1H,dd, J=9.1Hz),8.20(1H,dd,J=2.9Hz)
9	H	CH	2-Me	NMR($CDCl_3$) δ :1.86-1.94(2H,m),2.64(3H,s),2.83(2H,t,J=5.6Hz), 3.04(2H,t,J=5.6Hz),3.61(2H,t,J=5.6Hz),3.66(2H,t,J=5.6Hz),6.44 (1H,d,J=2.8Hz),6.52(1H,dd,J=2.8Hz,9.4Hz),8.09(1H,d,J=9.4Hz)
10	H	CH	2-CN	NMR($CDCl_3$) δ :1.84-2.05(2H,m),2.87(2H,t,J=5.4Hz),3.07(2H,t, J=5.4Hz),3.58-3.77(4H,m),6.81(1H,dd,J=2.9Hz,9.5Hz),6.97 (1H,d,J=2.9Hz),8.18(1H,d,J=9.5Hz)
11	H	CH	2-COOMe	NMR($CDCl_3$) δ :1.79-1.83(2H,m),2.74(2H,t,J=5.5Hz),2.95(2H,t, J=5.5Hz),3.50-3.59(4H,m),3.84(3H,s),6.56(1H,s),7.17(1H,d, J=8.2Hz),7.91(1H,d,J=8.2Hz)
12	Boc	CH	H	NMR($CDCl_3$) δ :1.40(9H,s),1.85-2.10(2H,m),3.19-3.35(2H,m),3.58-3.72(6H,m),6.71(2H,d,J=9.5Hz),8.12(2H,d,J=9.5Hz)
13	Boc	CH	3-F	NMR($CDCl_3$) δ :1.36(4H,s),1.43(5H,s),1.91-2.02(2H,m),3.35-3.48 (2H,m),3.59-3.72(6H,m),6.75-6.81(1H,m),7.86-7.95(2H,m)
14	Boc	N	H	NMR($CDCl_3$) δ :1.42(9H,s),1.80-2.09(2H,m),3.07-3.55(8H,m),4.47 (2H,s),6.61(4H,s),7.50-7.71(2H,m),7.82-7.94(3H,m),8.17(1H,s)
15	Boc	CH	3-Me	NMR($CDCl_3$) δ :1.52(9H,s),1.92-2.05(2H,m),2.37(3H,s),3.17-3.31 (4H,m),3.57-3.67(4H,m),7.02(1H,d,J=8.8Hz),7.96-8.04(2H,m)
16	Boc	CH	3-Cl	NMR($CDCl_3$) δ :1.53(9H,s),2.01-2.12(2H,m),3.39-3.49(2H,m),3.51-3.70(4H,m),7.05(1H,d,J=9.0Hz),8.03(1H,dd,2.5Hz,9.0Hz),8.24 (1H,d,J=2.5Hz)
17	Boc	CH	2-Me	NMR($CDCl_3$) δ :1.53(9H,s),1.94-2.02(2H,m),2.64(3H,s),3.23-3.38 (2H,m),3.59-3.66(6H,m),6.45(1H,d,J=2.5Hz),6.54(1H,dd, J=2.5Hz,9.1Hz),8.10(1H,d,J=9.1Hz)
18	Boc	CH	2-COOMe	NMR($CDCl_3$) δ :1.42(9H,s),1.91-2.02(2H,m),3.24-3.40(2H,m),3.58-3.70(6H,m),3.93(3H,s),6.64-6.74(2H,m),8.03(1H,d,J=9.1Hz)
21-1	Bn	CH	3-Cl	NMR($CDCl_3$) δ :1.98-2.06(2H,m),2.76(2H,d,J=5.5Hz),2.84(2H,t, J=5.1Hz),3.55-3.66(4H,m),3.67(2H,s),6.94(1H,d,J=9.2Hz),7.23-7.38(5H,m),8.01(1H,dd,J=3.0Hz,9.2Hz),8.21(1H,d,J=2.9Hz)

Table 10



Rf.	R_1	R_2	DATA
3	3-Py	H	NMR($CDCl_3$) δ :2.05-2.16(2H,m),3.35-3.48(4H,m), 3.51-3.58(2H,m),3.63-3.68(2H,m),4.48(2H,s), 6.52-6.58(2H,m),6.79(1H,d,J=8.9Hz),7.35(1H,d, J=8.9Hz),7.56-7.60(1H,m),7.63-7.69(2H,m),7.86-7.90(2H,m),8.20-8.27 (2H,m),8.70(1H,s)
19	Boc	H	NMR($CDCl_3$) δ :1.40(4H,s),1.42(5H,s),1.94-2.00(2H,m), 3.27-3.40(2H,m), 3.57-3.62(2H,m),3.71-3.93(4H,m), 6.50(1H,d,J=9.5Hz),8.20 (1H,dd,J=2.6Hz,9.5Hz),9.04(1H,d,J=2.6Hz)
20	Boc	3-Me	NMR($CDCl_3$) δ :1.45(4H,s),1.48(5H,s),1.82-1.95(2H,m), 2.23(3H,s),2.91-3.02(4H,m),3.44-3.59(4H,m),4.69(2H,s),6.41-6.46(1H,m),6.51(1H,s), 6.87(1H,d,J=8.5Hz),7.77(1H,dd,J=1.8Hz,8.4Hz),7.62-7.66(1H,m), 7.83-7.88(3H,m),8.16(1H,s)
21-2	Bn	3-Cl	NMR($CDCl_3$) δ :1.88-1.95(2H,m),2.70-2.82(4H,m),3.13-3.21(4H,m),3.69 (2H,s),4.48(2H,d,J=5.5Hz),6.48(1H,dd,J=2.9Hz,8.8Hz),6.68(1H,d, J=3.0Hz), 6.97(1H,d,J=8.8Hz),7.31-7.37(5H,m),7.58(1H,dd,J=1.8Hz, 8.4Hz),7.62(1H,dd,J=1.8Hz,8.8Hz),7.84-7.91(3H,m),8.18(1H,s)
21-3	Boc	3-Cl	NMR($CDCl_3$) δ :1.47(9H,s),1.91-2.00(2H,m),3.09-3.11(4H,m),3.56-3.61 (4H,m),4.49(2H,d,J=4.8Hz),6.47(1H,dd,J=2.5Hz,8.2Hz),6.68(1H,d,J= 2.5Hz),6.92(1H,d,J=8.2Hz),7.57-7.64(2H,m),7.84-7.92(3H,m),8.19(1H,s)
22	Boc	2-Me	NMR($CDCl_3$) δ :1.31(4H,s),1.44(5H,s),1.90-2.01(2H,m),2.21(3H,s),3.18-3.34(2H,m),3.40-3.58(6H,m),4.50(2H,s), 6.44-6.58(3H,m),7.58(1H,dd, J=1.9Hz,8.4Hz),7.68(1H,dd,J=1.9Hz,8.4Hz),7.84-7.92(3H,m),8.19(1H,s)
23	Boc	2-COOMe	NMR($CDCl_3$) δ :1.35(4H,s),1.49(5H,s),1.87-2.01(2H,m), 3.20-3.34(2H,m), 3.40-3.49(4H,m),3.51-3.58(2H,m),3.89(3H,s),4.61(2H,d,J=5.5Hz),6.55 (1H,d,J=9.1Hz), 6.82(1H,dd,J=2.5Hz,9.1Hz),7.32(1H,d,J=2.5Hz),7.57 (1H,dd,J=1.6Hz,8.5Hz),7.65(1H,dd,J=1.6Hz,8.5Hz),7.76-7.86(3H,m), 8.17(1H,s)

Table 11

Rf.	DATA
4	NMR($CDCl_3$) δ :1.92-2.25(2H,m),2.98(3H,s),3.30-3.58(8H,m),4.95(2H,s),6.40-6.68(4H,m),7.08 (2H,d,J=9.0Hz),7.56-7.88(4H,m),8.07-8.30(4H,m)
5	NMR($CDCl_3$) δ :1.39(3H,t,J=7.2Hz),2.01-2.07(2H,m),3.38-3.43(4H,m),3.57-3.64(4H,m),4.06 (2H,s),4.35(2H,q,J=7.2Hz),5.02(2H,s),6.50-6.52(2H,m),6.58(2H,d,J=8.8Hz),7.21 (2H,d,J=8.8Hz),7.57(1H,dd,J=1.6Hz,8.4Hz),7.83(1H,d,J=8.4Hz),7.87(1H,d,J=8.4Hz), 8.12(1H,s),8.20-8.22(2H,m)
6	NMR($CDCl_3$) δ :2.02(2H,m),3.29(2H,s),3.40-3.47(4H,m),3.61-3.66(4H,m),3.70(3H,s),5.03 (2H,s),6.52(2H,d,J=6.4Hz),6.57(2H,d,J=8.8Hz),6.83(2H,d,J=8.8Hz),7.59 (1H,dd,J=1.6Hz,8.4Hz),7.64(1H,dd,J=1.6Hz,8.4Hz),7.70(1H,s),7.84(1H,d,J=8.4Hz),7.89 (1H,d,J=8.4Hz),m),8.15(1H,s),8.22(2H,d,J=6.4Hz)
24	NMR($CDCl_3$) δ :1.30(4H,s),1.38(5H,s),1.84-1.94(2H,m),2.97(3H,s), 3.15-3.33(2H,m),3.44-3.56 (6H,m),4.94(2H,s),6.55(2H,d,J=9.2Hz),7.02-7.10(2H,m),7.58(1H,dd,J=1.9Hz,8.4Hz), 7.65-7.73(2H,m),7.84(1H,d,J=9.9Hz),7.84(1H,d,J=9.9Hz),8.13(1H,s)

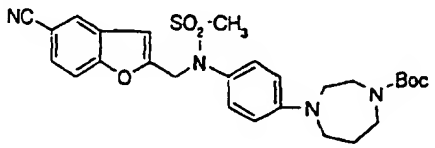
Table 12

Rf.	DATA
25	NMR($CDCl_3$) δ :1.35(4H,s),1.40(5H,s),1.85-1.96(5H,m),3.19-3.37(2H,m),3.47-3.58(6H,m),5.00 (2H,s),6.57(2H,d,J=9.2Hz),6.75-6.82(2H,m),7.55-7.67(3H,m),7.82(1H,d,J=8.6Hz), 7.88(1H,d,J=8.6Hz),8.15(1H,s)
26	NMR($CDCl_3$) δ :1.26(3H,t,J=7.3Hz),1.31(4H,s),1.39(5H,s),1.75-2.01(2H,m),3.13-3.31(2H,m), 3.45-3.57(6H,m),4.04(2H,s),4.35(2H,q,J=7.3Hz),5.02(2H,s),6.55(2H,d,J=9.0Hz),7.20 (2H,d,J=9.0Hz),7.50-7.92(5H,m),8.13(1H,s)
27	NMR($CDCl_3$) δ :1.29(9H,s),1.43(9H,s),1.79-1.88(2H,m),3.16-3.32(2H,m),3.46-3.53(6H,m), 5.19(2H,s),6.54(2H,d,J=9.0Hz),7.04-7.11(2H,m), 7.57(1H,dd,J=1.9Hz,9.0Hz), 7.65-7.70(2H,m),7.81-7.89(2H,m),8.13(1H,s)
28	NMR($CDCl_3$) δ :1.30(4H,s),1.37(3H,t,J=7.0Hz),1.39(5H,s),1.84-1.91(2H,m),3.15-3.21(1.4H,m) ,3.25-3.30(0.6H,m),3.44-3.51(6H,m),4.33(2H,q,J=7.0Hz),5.19(2H,s),6.54(2H,d,J=9.2Hz), 7.04-7.07(2H,m),7.57(1H,dd,J=1.4Hz,8.4Hz),7.65-7.70(2H,m),7.84(1H,d,J=8.4Hz), 7.87(1H,d,J=8.8Hz),8.13(1H,s),8.56-8.61(1H,m)
29	NMR($CDCl_3$) δ :1.35(4H,s),1.40(5H,s),1.86-1.92(2H,m),3.18-3.35(4H,m),3.47-3.55(6H,m),3.70 (3H,s),5.03(2H,s),6.55(2H,d,J=8.8Hz),6.79-6.85(2H,m),7.58(1H,dd,J=1.4Hz,8.4Hz),7.64 (1H,dd,J=1.4Hz,8.4Hz), 7.70(1H,s),7.84(1H,d,J=8.4Hz),7.86(1H,d,J=8.4Hz),8.15(1H,s)
30	NMR($CDCl_3$) δ :1.26(3H,t,J=7.4Hz),1.35(4H,s),1.41(5H,s),1.86-1.95(2H,m),2.40(2H,t,J=6.6Hz),2.64(2H,t,J=6.6Hz),3.20-3.26(1H,m),3.29-3.35(1H,m),3.47-3.56(6H,m),4.15(2H,q,J=7.4 Hz),5.00(2H,s),6.57(2H,d,J=8.8Hz), 6.63-6.68(2H,m),7.58(1H,dd,J=1.5Hz,8.5Hz),7.59(1H, dd,J=1.5Hz,8.5Hz),7.69(1H,s),7.82(1H,d,J=8.5Hz),7.88(1H,d,J=8.5Hz),8.15(1H,s)
31	NMR($CDCl_3$) δ :1.27(3H,t,J=7.2Hz),1.34(4H,s),1.40(5H,s),1.84-1.97(2H,m),3.17-3.35(2H,m), 3.45-3.57(6H,m),3.98(2H,d,J=6.0Hz),4.18(2H,q,J=7.2Hz),4.85(1H,t,J=6.0Hz),4.98(2H,s), 6.59(2H,d,J=9.0Hz),6.90-7.00(2H,m), 7.56(1H,dd,J=1.5Hz,8.4Hz),7.65(1H,d,J=9Hz), 7.69(1H,s),7.82(1H,d,J=8.4Hz),7.87(1H,d,J=8.4Hz),8.15(1H,s)
32	NMR($CDCl_3$) δ :1.38(3H,t,J=7.3Hz),1.45(5H,s),1.47(4H,s),1.84-1.96(2H,m),2.21(3H,s),2.94-3.06(4H,m),3.47-3.60(4H,m),3.93(2H,s),4.34(2H,q,J=7.3Hz),5.04(2H,s),6.92(2H,d,J=8.5Hz),7.13-7.18(3H,m),7.56-7.61(1H,m),7.82-7.88(2H,m),8.12(1H,s)
33	NMR($CDCl_3$) δ :1.38(3H,t,J=7.2Hz),1.45(9H,br),1.92-2.02(2H,m),3.08-3.14(4H,m),3.49-3.61 (4H,m),4.04(2H,s),4.35(2H,q,J=7.2Hz),5.03(2H,s),6.94(1H,d,J=8.5Hz),7.17(1H,dd,J=2.2Hz ,8.5Hz),7.43-7.47(2H,m),7.57(1H,dd,J=1.5Hz,8.5Hz),7.64-7.68(1H,m),7.827.90(2H,m), 8.14(1H,s)
34	NMR($CDCl_3$) δ :1.39-1.42(12H,m),1.78(3H,s),1.86-1.95(2H,m),3.18-3.27(2H,m),3.45-3.56 (6H,m),4.00(1H,d,J=14Hz),4.18(1H,d,J=14Hz),4.34(2H,q,J=7.0Hz),4.62(1H,d,J=14Hz), 5.19(1H,d,J=14Hz),6.34(1H,d,J=2.7Hz),6.54(1H,d,J=2.7Hz,8.8Hz),7.55-7.61(2H,m),7.67 (1H,dd,J=1.5Hz,8.4Hz),7.69(1H,d,J=1.5Hz),7.82(1H,d,J=8.4Hz),7.88(1H,d,J=8.4Hz), 8.10(1H,s)
35	NMR($CDCl_3$) δ :1.29-1.36(7H,m),1.41(5H,s),1.86-1.94(2H,m),3.17-3.32(2H,m),3.46-3.54 (6H,m),3.83(3H,s),4.08(2H,d,J=15.8Hz),4.26(2H,q,J=7.0Hz),4.82(1H,br),5.24(1H,br),6.59 (1H,dd,J=3.3Hz,8.8Hz),6.96-7.02(2H,m),7.10(1H,d,J=3.3Hz),7.58(1H,dd,J=1.4Hz,8.4Hz), 7.68-7.73(1H,m),7.82(1H,d,J=8.5Hz),7.88(1H,d,J=8.5Hz),8.12(1H,s)
36	NMR($CDCl_3$) δ :1.26(3H,t,J=7.2Hz),1.36(4H,s),1.41(5H,s),1.85-1.97(2H,m),3.22-3.38(2H,m), 3.47-3.60(6H,m),4.19(2H,q,J=7.2Hz),4.96(2H,s),6.61(2H,d,J=9.0Hz),6.77(1H,s),6.83(2H,d, J=8.4Hz),7.58(1H,dd,J=1.8Hz,8.4Hz),7.63-7.70(2H,m),7.83(1H,d,J=9.0Hz),7.89(1H,d, J=8.4Hz),8.14(1H,s)
37	NMR($CDCl_3$) δ :1.34(4H,s),1.39(3H,t,J=7.4Hz),1.40(5H,s),1.83-1.94(2H,m),3.32-3.45(6H,m), 3.49-3.57(2H,m),4.04(2H,s),4.35(2H,q,J=7.4Hz),5.01(2H,s),6.68-6.75(1H,m),7.00-7.10 (2H,m),7.58(1H,dd,J=1.9Hz,8.5Hz),7.64-7.68(2H,m),7.84(1H,d,J=8.4Hz),7.87(1H,d,J=8.4 Hz),8.14(1H,s)

Table 13

Rf.	DATA
38	NMR($CDCl_3$) δ :1.34-1.41(12H,m),1.84-1.91(2H,m),3.20-3.34(2H,m),3.48-3.61(4H,m),3.68-3.72(2H,m),4.06(2H,s),4.35(2H,q,J=6.9Hz),5.00(2H,s),6.36(1H,d,J=9.2Hz),7.27-7.39(1H,m),7.58(1H,dd,J=1.7Hz,8.6Hz),7.65-7.70(2H,m),7.85(1H,d,J=8.1Hz),7.88(1H,d,J=8.1Hz),8.13-8.15(2H,m)
39	NMR($CDCl_3$) δ :1.24(3H,t,J=7.2Hz),1.30(9H,s),1.38(9H,s),1.82-1.94(2H,m),3.14-3.31(2H,m),3.44-3.54(6H,m),4.08(2H,s),4.16(2H,q,J=7.2Hz),5.16(2H,s),6.52(2H,d,J=9.0Hz),7.01-7.07(2H,m),7.56(1H,dd,J=1.9Hz,9.0Hz),7.65-7.70(2H,m),7.81-7.89(2H,m),8.12(1H,s)

Table 14



Rf.	DATA
40	NMR($CDCl_3$) δ :1.35(s,4H),1.41(s,5H),1.87-1.97(m,2H),2.98(s,3H),3.18-3.27(m,1H),3.27-3.36(m,1H),3.48-3.60(m,6H),4.93(s,2H),6.60(d,2H,J=9.0Hz),6.65(s,1H),7.08(d,2H,J=9.0Hz),7.54-7.57(m,2H),7.85(s,1H)

Table 15

Ex	DATA
1	NMR(DMSO-d_6) δ :1.80-1.90(2H,m),3.05(3H,s),3.42-3.46(2H,m),3.56-3.63(2H,m),3.85-3.90(4H,m),4.97(2H,s),6.66(2H,d,J=9.2Hz),7.02-7.11(2H,m),7.15(2H,d,J=9.2Hz),7.62(1H,dd,J=1.9Hz,8.8Hz),7.79(1H,dd,J=1.9Hz,8.8Hz),7.91(1H,s),8.00(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.12-8.17(2H,m),8.46(1H,s),9.19(3H,br),9.46(2H,br)
2	NMR(DMSO-d_6) δ :1.27(3H,t,J=6.8Hz),1.82-1.89(2H,m),3.42-3.46(2H,m),3.60-3.63(4H,m),3.83-3.86(2H,m),4.24(2H,q,J=6.8Hz),4.33(2H,s),4.98(2H,s),6.82(2H,d,J=9.2Hz),7.03-7.10(2H,m),7.15(2H,d,J=9.2Hz),7.60(1H,dd,J=1.6Hz,8.8Hz),7.82(1H,dd,J=1.6Hz,8.8Hz),7.89(1H,s),8.01(1H,d,J=8.8Hz),8.11(1H,d,J=8.8Hz),8.12-8.16(2H,m),8.48(1H,s),9.31(2H,s),9.52(2H,s),13.68(1H,br)
3	NMR(DMSO-d_6) δ :1.81-1.88(2H,m),3.21(2H,s),3.44-3.47(2H,m),3.57(3H,s),3.60-3.66(4H,m),3.84-3.86(2H,m),4.99(2H,s),6.69(2H,d,J=9.2Hz),6.93(2H,d,J=9.2Hz),7.02-7.10(2H,m),7.57(1H,dd,J=1.6Hz,8.4Hz),7.82(1H,dd,J=1.6Hz,8.4Hz),7.87(1H,s),8.02(1H,d,J=8.4Hz),8.12(1H,d,J=8.4Hz),8.13-8.17(2H,m),8.45(1H,s),9.29(2H,s),9.53(2H,s),13.66(1H,br)
4	NMR(DMSO-d_6) δ :1.83-1.89(2H,m),3.42-3.45(2H,m),3.59-3.63(4H,m),3.83-3.86(2H,m),4.22(2H,s),4.98(2H,s),6.69(2H,d,J=8.8Hz),7.03-7.09(2H,m),7.15(2H,d,J=8.8Hz),7.61(1H,dd,J=1.6Hz,8.4Hz),7.83(1H,dd,J=1.6Hz,8.4Hz),7.89(1H,s),8.01(1H,d,J=8.4Hz),8.11(1H,d,J=8.4Hz),8.12-8.15(2H,m),8.50(1H,s),9.37(2H,s),9.55(2H,s),13.76(1H,br)
5	NMR(DMSO-d_6) δ :1.82-1.89(2H,m),3.12(2H,s),3.45-3.48(2H,m),3.60-3.66(4H,m),3.84-3.87(2H,m),4.99(2H,s),6.70(2H,d,J=8.8Hz),6.95(2H,d,J=8.8Hz),7.02-7.09(2H,m),7.58(1H,dd,J=1.6Hz,8.4Hz),7.84(1H,dd,J=1.6Hz,8.4Hz),7.90(1H,s),8.02(1H,d,J=8.8Hz),8.11-8.16(3H,m),8.48(1H,s),9.39(2H,s),9.58(2H,s),13.80(1H,br)
6	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.0Hz),2.01-2.07(2H,m),3.03-3.06(2H,m),3.11-3.15(2H,m),3.41(2H,t,J=6.0Hz),3.62-3.65(2H,m),4.24(2H,q,J=7.0Hz),4.36(2H,s),5.01(2H,s),6.68(2H,d,J=9.2Hz),7.20(2H,d,J=9.2Hz),7.66(1H,dd,J=1.7Hz,8.6Hz),7.82(1H,dd,J=1.7Hz,8.6Hz),7.90(1H,s),8.02(1H,d,J=8.6Hz),8.10(1H,d,J=8.6Hz),8.49(1H,s),9.27(2H,br),9.31(2H,s),9.52(2H,s)

Table 16

Ex	DATA
7	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.0Hz),2.01-2.08(2H,m),2.99-3.06(2H,m),3.08-3.15(2H,m), 3.34-3.42(2H,m),3.59-3.65(2H,m),3.81(2H,d,J=5.2Hz),4.18(2H,q,J=7.0Hz),4.91(2H,s),6.63 (2H,d,J=9.0Hz),7.16(2H,d,J=9.0Hz),7.66(1H,dd,J=1.5Hz,8.4Hz),7.81(1H,dd,J=1.5Hz, 8.4Hz),7.88(1H,s),7.96-8.01(2H,m),8.08(1H,d,J=8.8Hz),8.45(1H,s),9.42(4H,br),9.53(2H,br)
8	NMR(DMSO-d_6) δ :1.16(3H,t,J=7.0Hz),2.02-2.09(2H,m),3.01-3.06(2H,m),3.10-3.15(2H,m), 3.28(2H,s),3.43(2H,t,J=7.0Hz),3.63-3.67(2H,m),4.04(2H,q,J=7.0Hz),5.03(2H,s),6.69(2H,d, J=9.1Hz),7.00(2H,d,J=9.1Hz),7.63(1H,dd,J=1.6Hz,9.6Hz),7.81(1H,dd,J=1.6Hz,8.6Hz),7.87 (1H,s),8.04(1H,d,J=8.6Hz),8.12(1H,d,J=8.6Hz),8.45(1H,s),9.29(4H,s),9.53(2H,s)
9	NMR(DMSO-d_6) δ :1.18(3H,t,J=7.0Hz),1.89-1.96(2H,m),2.35(2H,t,J=7.0Hz),2.53(2H,t, J=7.0Hz),2.89(2H,t,J=5.6Hz),3.02(2H,t,J=5.2Hz),3.44(2H,t,J=6.2Hz),3.56(2H,t,J=5.2Hz), 4.06(2H,q,J=7.0Hz),4.99(2H,s),6.67(2H,d,J=9.2Hz),6.99(2H,d,J=9.2Hz),7.61(1H,dd, J=1.6Hz, 8.2Hz),7.79(1H,dd,J=1.6Hz,8.2Hz),7.84(1H,s),8.01(1H,d,J=8.6Hz),8.11(1H,d, J=8.6Hz),8.44(1H,s),9.52(6H,br)
10	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),1.95-2.04(2H,m),2.21(3H,s),3.02(2H,t,J=5.5Hz), 3.16-3.26(6H,m),4.23(2H,q,J=7.0Hz),4.41(2H,s),5.06(2H,s),7.02(1H,d,J=8.8Hz),7.17 (1H,dd,J=2.4Hz,8.8Hz),7.28(1H,d,J=2.4Hz), 7.64-7.68(1H,m),7.80-7.84(1H,m),7.93(1H,s), 8.02(1H,d,J=8.5Hz),8.10(1H,d,J=8.5Hz),8.49(1H,s),9.34(2H,br),9.41(2H,br),9.54(2H,br)
11	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),2.03-2.10(2H,m),3.13-3.22(4H,m),3.27(2H,t,J=6.8Hz), 3.42-3.46(2H,m),4.23(2H,q,J=7.0Hz),4.45(2H,s),5.06(2H,s),6.84-6.89(1H,m),7.11(1H,dd, J=2.8Hz,9.2Hz),7.28(1H,dd,J=2.8Hz,14.4Hz),7.66(1H,dd,J=1.6Hz,8.8Hz),7.80(1H,dd, J=1.6Hz,8.8Hz),7.94(1H,s),8.02(1H,d,J=8.8Hz), 8.10(1H,d,J=8.8Hz),8.48(1H,s),9.15 (2H,br),9.23(2H,s),9.49(2H,s)
12	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.3Hz),2.00-2.03(2H,m),3.14-3.28(6H,m),3.31-3.36(2H,m), 4.23(2H,q,J=7.3Hz),4.50(2H,s),5.04(2H,s),7.14(1H,d,J=8.8Hz),7.32(1H,dd,J=2.3Hz,8.8Hz) ,7.53(1H,d,J=2.3Hz),7.64-7.68(1H,m),7.82(1H,dd,J=1.9Hz,8.5Hz),7.94(1H,s),8.03(1H,d, J=8.5Hz),8.10(1H,d,J=8.5Hz),8.49(1H,s),9.32(4H,br),9.51(2H,br)
13	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),1.83(3H,s),2.02-2.10(2H,m),3.01-3.09(2H,m),3.11-3.17 (2H,m),3.40-3.46(2H,m),3.63-3.71(2H,m),4.24(2H,q,J=7.0Hz),4.32(1H,d,J=14.3Hz),4.52 (1H,d,J=14.3Hz),4.68(1H,d,J=14.3Hz),5.12(1H,d,J=14.3Hz),6.47(1H,d,J=2.7Hz),6.65(1H, dd,J=2.7Hz,8.8Hz),7.38(1H,d,J=8.8Hz),7.64(1H,dd,J=1.6Hz,8.4Hz),7.80(1H,s),7.84(1H,dd, J=1.6Hz,8.4Hz),8.02(1H,d,J=8.4Hz),8.11(1H,d,J=8.4Hz),8.47(1H,s),9.40(4H,br),9.55 (2H,br)
14	NMR(DMSO-d_6) δ :2.01-2.09(2H,m),3.03-3.10(2H,m),3.11-3.19(2H,m),3.41-3.48(2H,m),3.65-3.70(2H,m),3.71(3H,s),3.72(3H,s),4.39(2H,d,J=4.8Hz),4.97(2H,br),6.85(1H,dd,J=2.9Hz,8.8 Hz),6.97(1H,d,J=2.9Hz),7.19(1H,d,J=8.8Hz), 7.71(1H,dd,J=1.5Hz,8.4Hz),7.82(1H,dd,J=1.5 Hz,8.4Hz),7.88(1H,s),8.01(1H,d,J=8.4Hz),8.10(1H,d,J=8.4Hz),8.45(1H,s),9.28(4H,br),9.52 (2H,br)
15	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.92-2.04(2H,m),3.08-3.18(4H,m),3.56-3.61(2H,m), 3.81-3.85(2H,m),4.24(2H,q,J=7.2Hz),4.47(2H,s),5.04(2H,s),6.68(1H,d,J=8.8Hz),7.60 (1H,d,J=8.8Hz),7.67(1H,dd,J=1.6Hz,8.8Hz),7.81(1H,dd,J=1.6Hz,8.4Hz),7.95(1H,s), 8.02-8.06(2H,m),8.11(1H,d,J=8.8Hz),8.48(1H,s),8.98(2H,br),9.15(2H,s),9.46(2H,s)
16	NMR(DMSO-d_6) δ :1.77-1.87(2H,m),2.01(1.8H,s),2.24(1.2H,s),3.09(3H,s),3.44-3.76(8H,m), 4.98(2H,s),6.65-6.73(2H,m),7.16-7.23(2H,m),7.63-7.68(1H,m),7.78-7.84(1H,m),7.89-7.93 (1H,m),7.99-8.04(1H,m),8.09(1H,d,J=8.8Hz),8.49(0.4H,s),8.51(0.6H,s),8.61(0.6H,s),8.75 (0.4H,s),9.24-9.32(3H,m),9.51(2H,s)
17	NMR(DMSO-d_6) δ :1.78-1.87(5H,m),2.01(2H,s),2.25(1H,s),3.48-3.88(8H,m),4.99(2H,s),6.68-6.75(2H,m),6.95-7.03(2H,m),7.55-7.61(1H,m),7.79-7.87(2H,m),7.99-8.04(1H,m),8.11(1H,d, J=8.9Hz),8.49(0.3H,s),8.53(0.7H,s),8.64(0.7H,s), 8.78(0.3H,s),9.27-9.35(3H,m),9.50-9.56 (2H,s) MS(m/z):457($M-2HCl+1)^+$

Table 17

Ex	DATA
18	NMR(DMSO-d_6) δ :1.82-1.88(2H,m),2.03(2H,s),2.26(1H,s),3.45-3.71(8H,m),4.86(2H,s),6.72 (2H,br),7.13-7.20(3H,m),7.71(1H,d,J=8.6Hz),7.81-7.86(1H,m),7.91(1H,d,J=8.6Hz),8.00 (1H,d,J=8.6Hz),8.02(1H,d,J=8.6Hz),8.06-8.11(1H,m),8.74(1H,s),9.49(4H,br),9.63(2H,br)
19	NMR(DMSO-d_6) δ :1.28(3H,t,J=7.0Hz),1.78-1.85(2H,m),2.07(1.8H,s),2.33(1.2H,s),3.45-3.59 (5H,m),3.63-3.74(3H,m),4.15(2H,q,J=7.0Hz),5.12(1.2H,s),5.13(0.8H,s),6.69-6.74(2H,m), 7.06-7.10(2H,m),7.62-7.65(1H,m),7.81-7.84(1H,m),7.91(1H,s),8.02-8.05(1H,m),8.11 (1H,d,J=8.6Hz),8.49(0.4H,s),8.52(0.6H,s),8.67(0.6H,s),8.80(0.4H,s),9.31(2H,s),9.38(1H,s), 9.53(0.8H,s),9.54(1.2H,s),11.44(1H,s)
20	NMR(DMSO-d_6) δ :1.21(3H,t,J=7.0Hz),1.79-1.90(2H,m),2.09(2H,s),2.26(1H,s),3.40-3.80 (10H,m),4.11(2H,q,J=7.0Hz),4.94(2H,s),5.87(0.7H,t,J=5.9Hz),5.93(0.3H,t,J=5.9Hz), 6.70-6.77(2H,m),6.97-7.04(2H,m),7.59-7.64(1H,m),7.78-7.85(2H,m),7.99-8.04(1H,m),8.11 (1H,d,J=8.6Hz),8.44(0.7H,s),8.48(0.3H,s),8.62(0.7H,s),8.75(0.3H,s),9.22(2H,s),9.33(1H,s), 9.46-9.53(2H,m)
21	NMR(DMSO-d_6) δ :1.13(3H,t,J=7.0Hz),1.78-1.90(2H,m),2.07(2H,s),2.28(1H,s),3.48-3.83 (8H,m),4.01(2H,q,J=7.5Hz),4.95-5.01(2H,m),6.77(2H,d,J=8.6Hz),6.96-7.06(2H,m), 7.56-7.62(1H,m),7.82-7.91(2H,m),7.99-8.05(1H,m),8.11(1H,d,J=8.6Hz),8.49-8.64(2H,m), 8.79(0.7H,s),8.95(0.3H,s),9.44(2H,s),9.54(1H,s),9.59-9.66(2H,m)
22	NMR(DMSO-d_6) δ :1.25-1.29(3H,m),1.79-1.85(2H,m),2.03(2H,s), 2.25(1H,s),3.47-3.75(8H,m), 4.21-4.27(2H,m),4.37(2H,s), 5.00(2H,s),6.68-6.73(2H,m),7.17-7.21(2H,m),7.62-7.66(1H,m) , 7.82(1H,d,J=8.8Hz),7.90(1H,s),8.03(1H,dd,J=4.0Hz,8.8Hz),8.10(1H,d,J=8.8Hz),8.49 (0.4H,s),8.51(0.6H,s),8.64(0.6H,s),8.76(0.4H,s),9.29(2H,s),9.33(1H,s),9.53(2H,s) MS(m/z):565(M-2HCl+1)*
23	NMR(DMSO-d_6) δ :1.22(3H,t,J=7.0Hz),1.80-1.86(2H,m),2.01(2H,s), 2.25(1H,s),3.49-3.54 (6H,m),3.66(2H,s),3.71-3.82(2H,m),4.13(2H,q,J=7.0Hz),4.90(2H,s), 6.66-6.75(2H,m),7.16-7.20(2H,m),7.62-7.67(1H,m),7.82-7.89(2H,m),8.08-8.11(2H,m),8.51(1H,s), 8.74(1H,s),9.43 (4H,br),9.62(2H,br) MS(m/z):580(M-2HCl+1)*
24	NMR(DMSO-d_6) δ :1.13-1.18(3H,m),1.78-1.85(2H,m),2.03(2H,s),2.25(1H,s),3.26(1.4H,s),3.28 (0.6H,s),3.48-3.54(4H,m), 3.58-3.72(4H,m),4.00-4.07(2H,m),5.02(2H,s),6.69-6.73(2H,m), 6.69-7.01(2H,m),7.60-7.63(1H,m),7.80-7.83(1H,m),7.86(0.7H,s), 7.88(0.3H,s),8.04(1H,d, J=8.4Hz),8.12(1H,d,J=8.4Hz),8.45(0.3H,s),8.48(0.7H,s),8.60(0.7H,bs),8.74(0.3H,bs),9.24 (2H,br),9.28(1H,br),9.52(2H,s) MS(m/z):529(M-2HCl+1)*
25	NMR(DMSO-d_6) δ :1.18(3H,t,J=7.0Hz),1.81-1.86(2H,m),2.01(2H,s),2.25(1H,s),2.29-2.36 (2H,m),2.52-2.57(2H,m),3.50-3.56(3H,m),3.58-3.62(1H,m),3.65-3.76(4H,m),4.06 (2H,q,J=7.0Hz),4.99(2H,s),6.71-6.76(2H,m),6.97-7.02(2H,m),7.56-7.58(1H,m),7.79-7.85 (2H,m),8.02(1H,d,J=8.6Hz),8.11(1H,d,J=8.6Hz),8.46(0.3H,s),8.49(0.7H,s),8.62(0.7H,s), 8.76(0.3H,s),9.27(2H,s),9.37(1H,s),9.52(2H,s)
26	NMR(DMSO-d_6) δ :1.26(3H,t,J=7.0Hz),1.86-1.97(2H,m),2.14-2.21(3H,brs),2.27(2H,s),2.34 (1H,s),2.97-3.03(2H,br),3.10-3.17(2H,m),3.66-3.75(4H,m),4.23(2H,q,J=7.0Hz),4.43 (2H,brs),5.07(2H,s),6.96-7.04(1H,m),7.19(1H,dd,J=2.1Hz,8.0Hz),7.27-7.30(1H,br),7.66 (1H,dd,J=1.4Hz,8.4Hz),7.85(1H,dd,J=1.4Hz,8.4Hz),7.93(1H,s),8.03(1H,d,J=8.6Hz), 8.09(1H,d,J=8.6Hz),8.53(1H,s),8.78(0.6H,s),8.85(0.4H,s),9.44(3H,s),9.61(2H,s)
27	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.0Hz),1.90-2.00(2H,m),2.25(2H,s),2.32(1H,s),3.09-3.18 (2H,m),3.20-3.40(2H,m),3.64-3.74(4H,m),4.22(2H,q,J=7.0Hz),4.51(2H,s),5.04(2H,s),7.12 (0.4H,d,J=8.8Hz),7.14(0.6H,d,J=8.8Hz),7.33(1H,dd,J=2.5Hz,8.8Hz),7.54(1H,d,J=2.5Hz), 7.64-7.68(1H,m),7.83(1H,dd,J=1.8Hz,8.4Hz),7.94(1H,s),8.03(1H,d,J=8.5Hz),8.10 (1H,d,J=8.5Hz),8.51(1H,s),8.74(0.6H,s),8.77(0.4H,s),9.37(3H,br),9.56(2H,br)

Table 18

Ex	DATA
28	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.5Hz),1.78(2H,s),1.82(1H,s),1.83(2H,br),2.10(2H,s),2.29 (1H,s),3.50-3.61(5H,m),3.70(2H,br),3.79(1H,br),4.25(2H,q,J=7.5Hz),4.34(1H,d,J=14.0Hz), 4.54(1H,d,J=14.0Hz),5.13(2H,d,J=14.0Hz),6.54(1H,br),6.69(1H,br),7.37-7.40(1H,m), 7.58-7.63(1H,m),7.78(1H,s),7.86-7.92(1H,m),8.02-8.06(1H,m),8.09-8.14(1H,m),8.47(1H,s), 8.57(0.6H,s),8.79(0.4H,s),9.48(2H,s),9.56(1H,br),9.67(2H,s)
29	NMR(DMSO-d_6) δ :1.82(2H,br),2.11(2H,s),2.27(1H,s),3.51-3.59(8H,m),3.72(6H,s),4.43(2H,br) 4.91(1H,d,J=14.5Hz),5.13(1H,d,J=14.5Hz),6.86-6.92(1H,m),6.99(1H,br),7.14 (1H,d,J=9.1Hz),7.18(1H,d,J=9.1Hz),7.66-7.74(1H,m),7.87(1H,br),8.00-8.04(1H,m), 8.08-8.14(1H,m),8.54(1H,s),8.84(0.6H,s),8.98(0.4H,s),9.47(2H,s),9.55(1H,br),9.75(2H,br)
30	NMR(DMSO-d_6) δ :1.78-1.84(2H,m),2.03(2H,s),2.25(1H,s),3.28(1.3H,s),3.30(0.7H,s), 3.49-3.55(4H,m),3.57(1H,s),3.58(2H,s),3.60-3.75(4H,m),5.01(2H,s),6.70-6.73(2H,m), 6.96-7.00(2H,m),7.57-7.62(1H,m),7.81-7.91(2H,m),8.04(1H,d,J=8.6Hz),8.12(1H,d, J=8.6Hz),8.47(0.3H,s),8.51(0.7H,s),8.65(0.7H,s),8.80(0.3H,s),9.30(3H,br),9.55(2H,s)
31	NMR(DMSO-d_6) δ :1.82-1.89(2H,m),2.09(1.5H,s),2.28(1.5H,s),3.29-3.35(2H,m),3.39-3.42 (1H,m),3.47-3.50(1H,m), 3.60-3.70(3H,m),3.72-3.78(1H,m),4.33(2H,s),5.05(2H,s),6.86-6.92(1H,m),7.08-7.12(1H,m),7.25-7.29(1H,m),7.66(1H,dd,J=1.6Hz,8.6Hz),7.83(1H,d,J=8.6 Hz),7.93(1H,s),8.03(1H,d,J=8.6Hz),8.10(1H,d,J=8.6Hz),8.51(1H,s),8.73(1H,br),9.33(3H,br) ,9.53(2H,s)
32	NMR(DMSO-d_6) δ :1.79-1.83(2H,m),2.12(1.8H,s),2.25(1.2H,s),3.53-3.60(2H,m),3.64-3.70 (3H,m),3.73-3.82(2H,m), 3.84-3.88(1H,m),4.39(2H,s),5.04(2H,s),6.79-6.86(1H,m),7.64-7.69(2H,m),7.84(1H,dd,J=2.0Hz,10.2Hz),7.94(1H,s),8.01-8.06(2H,m),8.12(1H,d,J=11.3Hz) ,8.53(0.6H,s),8.54(0.4H,s),8.73(0.6H,s),8.82(0.4H,s),9.36(2H,s),9.41(0.4H,s),9.43(0.6H,s), 9.57(2H,s) MS(m/z):538(M-2HCl+1)$^+$
33	NMR(DMSO-d_6) δ :1.79-1.86(2H,m),2.03(2H,s),2.26(1H,s), 3.49-3.79(8H,m),4.26(2H,s),5.00 (1.4H,s),5.01(0.6H,s), 6.70-6.74(2H,m),7.18-7.22(2H,m),7.63-7.67(2H,m), 7.84-7.90(1H,m) ,8.02(0.3H,d,J=8.4Hz),8.03(0.7H,d,J=8.4Hz), 8.10(1H,d,J=8.4Hz),8.54(0.3H,s),8.57 (0.7H,s),8.75(0.7H,s), 8.92(0.3H,s),9.45(2H,s),9.48(1H,s),9.62(0.6H,s),9.63(1.4H,s) MS(m/z):537(M-2HCl+1)$^+$
34	NMR(DMSO-d_6) δ :1.80-1.87(2H,m),2.01(2H,s),2.25(1H,s), 3.46-3.56(4H,m),3.63-3.71(2H,m), 3.73(2H,s),3.75-3.79(2H,m),4.89(2H,s),6.76-6.84(2H,m), 7.13-7.20(2H,m),7.65(1H,dd,J= 3.8Hz,8.1Hz), 7.82-7.94(3H,m),8.01(1H,d,J=8.1Hz),8.08(1H,d,J=8.6Hz), 8.65(1H,s),9.42 (4H,br),9.61(2H,br)
35	NMR(DMSO-d_6) δ :1.78-1.86(2H,m),2.03(2H,s),2.25(1H,s), 3.17(1.4H,s),3.19(0.6H,s), 3.49-3.55(4H,m),3.59-3.74(4H,m),5.02(2H,s),6.70-6.74(2H,m),6.97-7.02(2H,m),7.60-7.62 (1H,m),7.78-7.83(1H,m),7.90(0.7H,s),7.92(0.3H,s),8.03(1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz) ,8.45(0.7H,s),8.48(0.7H,s),8.61(0.7H,s),8.75(0.3H,s),9.27(3H,br),9.53(2H,s)
36	NMR(DMSO-d_6) δ :1.80-1.82(2H,m),2.04(2H,s),2.25(1H,s),2.26-2.33(2H,m),2.46-2.52(2H,m), 3.48-3.75(8H,m),4.99(2H,s),6.71-6.74(2H,m),6.99-7.06(2H,m),7.56-7.59(1H,m),7.95-7.82 (1H,m),7.86(1H,br),8.00(1H,d,J=9.2Hz), 8.12(1H,d,J=9.2Hz),8.44(0.3H,s),8.45(0.7H,s), 8.53(0.7H,br),8.65(0.3H,br),9.17(3H,br),9.47(2H,s), MS(m/z):515(M-2HCl+1)$^+$
37	NMR(DMSO-d_6) δ :1.78-1.92(2H,m),2.08(2H,s),2.33(1H,s),3.47-3.82(10H,m),4.94(2H,s), 5.70-5.90(1H,m),6.78(2H,d,J=7.5Hz),6.98-7.07(2H,m),7.62(1H,d,J=8.5Hz),7.80-7.87 (2H,m),7.98-8.04(1H,m),8.10(1H,d,J=8.9Hz),8.47(0.3H,s), 8.52(0.7H,s),8.73(0.7H,s),8.90 (0.3H,s),9.39(2H,s),9.49(1H,s),9.54-9.62(2H,m)
38	NMR(DMSO-d_6) δ :1.86-1.96(2H,m),2.18(3H,br),2.26(2H,s),2.33(1H,s),2.98(2H,br),3.12 (2H,br),3.66-3.71(4H,m),4.29(2H,br),5.06(2H,s),6.98-7.02(1H,m),7.19(1H,d,J=6.0Hz),7.29 (1H,br),7.66(1H,d,J=8.8Hz),7.82(1H,dd,J=1.6Hz,8.8Hz),7.94(1H,s),8.02(1H,d,J=8.8Hz), 8.09(1H,d,J=8.8Hz),8.51(1H,s),8.70(0.6H,s),8.76(0.4H,s),9.35(3H,s),9.54(2H,s)

Table 19

Ex	DATA
39	NMR(DMSO-d_6) δ :1.82(2H,br),2.11(2H,s),2.27(1H,s),3.51-3.59(8H,m),3.72(6H,s),4.43 (2H,br),4.91(1H,d,J=14.5Hz),5.13(1H,d,J=14.5Hz),6.86-6.92(1H,m),6.99(1H,br),7.14 (1H,d,J=9.1Hz),7.18(1H,d,J=9.1Hz),7.66-7.74(1H,m),7.87(1H,br),8.00-8.04(1H,m), 8.08-8.14(1H,m),8.54(1H,s),8.84(0.6H,s),8.98(0.4H,s),9.47(2H,s),9.55(1H,br),9.75(2H,br)
40	NMR(DMSO-d_6) δ :1.99-2.06(2H,m),3.03-3.08(2H,m),3.12-3.16(2H,m),3.41(2H,t,J=6.0Hz), 3.61-3.65(2H,m),4.23(2H,s),5.01(2H,s),6.68(2H,d,J=9.1Hz),7.21(2H,d,J=9.1Hz),7.66 (1H,dd,J=1.6Hz,8.6Hz),7.79-7.82(1H,m),7.91(1H,s),8.02(1H,d,J=8.6Hz),8.10 (1H,d,J=8.6Hz),8.47(1H,s),9.12(2H,br),9.23(2H,br),9.48(2H,s)
41	NMR(DMSO-d_6) δ :2.01-2.07(2H,m),3.03-3.08(2H,m),3.12-3.16(2H,m),3.20(2H,s),3.43 (2H,t,J=5.9Hz),3.63-3.67(2H,m),5.03(2H,s),6.70(2H,d,J=9.2Hz),7.02(2H,d,J=9.2Hz),7.63 (1H,dd,J=1.6Hz,8.6Hz),7.81(1H,dd,J=1.6Hz,8.6Hz),7.91(1H,s),8.02(1H,d,J=8.6Hz),8.12 (1H,d,J=8.6Hz),8.44(1H,s),9.16(2H,br),9.23(2H,s),9.50(2H,s)
42	NMR(DMSO-d_6) δ :2.00-2.06(2H,m),2.32(2H,t,J=6.4Hz),2.51(2H,t,J=6.4Hz),3.06-3.11(2H,m), 3.15-3.19(2H,m),3.40-3.46(2H,m),3.61-3.66(2H,m),5.00(2H,s),6.71(2H,d,J=8.8Hz),7.03 (2H,d,J=8.8Hz),7.58(1H,dd,J=1.6Hz,8.6Hz),7.78(1H,dd,J=1.6Hz,8.6Hz),7.86(1H,s),8.00 (1H,d,J=8.6Hz),8.11(1H,d,J=8.6Hz),8.43(1H,s),8.93(2H,br),9.12(2H,s),9.45(2H,s)
43	NMR(DMSO-d_6) δ :1.26(1H,t,J=7.0Hz),1.83-1.89(2H,m),2.09(1.5H,s),2.29(1.5H,s),3.30-3.36 (2H,m),3.40-3.43(1H,m),3.47-3.51(1H,m),3.61-3.70(3H,m),3.76-3.80(1H,m),4.23 (2H,q,J=7.0Hz),4.47(2H,s),5.06(2H,s),6.87-6.93(1H,m),7.07-7.11(1H,m),7.25-7.29(1H,m), 7.65(1H,d,J=8.6Hz),7.84(1H,d,J=8.6Hz),7.93(1H,s),8.07(1H,d,J=8.0Hz),8.10(1H,d, J=8.0Hz),8.52(0.5H,s),8.54(0.5H,s),8.80(0.5H,s),8.82(0.5H,s),9.41-9.46(3H,m),9.59(2H,br)
44	NMR(DMSO-d_6) δ :1.24-1.28(3H,m),1.78-1.85(2H,m),2.12(18H,s),2.25(1.2H,s),3.53-3.61 (2H,m),3.64-3.70(3H,m),3.74-3.81(2H,m),3.84-3.88(1H,m),4.22-4.27(2H,m),4.52(2H,s), 5.04(2H,s),6.78-6.86(1H,m),7.64-7.68(2H,m),7.84(1H,d,J=8.6Hz),7.93(1H,s),8.02-8.06 (2H,m),8.12(1H,d,J=8.6Hz),8.53(0.6H,s),8.55(0.4H,s),8.75(0.6H,br),8.84(0.4H,br), 9.34-9.46(3H,m),9.58(2H,br)
45	NMR(DMSO-d_6) δ :2.01-2.07(2H,m),3.02-3.07(4H,m),3.11-3.16(2H,m),3.41-3.45(2H,m),3.64-3.67(2H,m),5.03(2H,s),6.69(2H,t,J=9.3Hz),6.95(1H,s),7.04(2H,d,J=9.3Hz),7.39(1H,s),7.64 (1H,dd,J=1.2Hz,8.8Hz),7.80(1H,dd,J=1.2Hz,8.4Hz),7.94(1H,s),8.02(1H,d,J=8.4Hz),8.14 (1H,d,J=8.8Hz),8.43(1H,s),9.17(2H,s),9.23(2H,s),9.51(2H,s)
46	NMR(DMSO-d_6) δ :0.99(3H,t,J=3.0Hz),2.01-2.07(2H,m),3.01-3.08(6H,m),3.41-3.44(2H,m), 3.63-3.67(2H,m),5.02(2H,s),6.68(2H,d,J=9.0Hz),7.02(2H,d,J=9.0Hz),7.64(1H,dd,J=1.6Hz, 8.0Hz),7.80(1H,dd,J=1.6Hz,8.8Hz),7.88-7.91(2H,m),8.02(1H,d,J=8.8Hz),8.13 (1H,d,J=8.0Hz),8.43(1H,s),9.14-9.24(4H,m),9.50(2H,s)
47	NMR(DMSO-d_6) δ :0.83(3H,t,J=6.8Hz),0.98(3H,t,J=6.8Hz),1.93-2.00(2H,m),2.88-2.92(2H,m), 3.00-3.10(4H,m),3.18-3.42(6H,m),3.56-3.60(2H,m),5.02(2H,s),6.34(2H,d,J=8.8Hz), 6.99(2H,d,J=8.8Hz),7.70(1H,dd,J=1.4Hz,8.3Hz),7.80(1H,dd,J=2.0Hz,8.8Hz),7.91(1H,s), 8.03(1H,d,J=8.3Hz),8.12(1H,d,J=8.8Hz),8.41(1H,s)
48	NMR(DMSO-d_6) δ :1.15(3H,t,J=6.8Hz),2.01-2.11(2H,m),3.02-3.20(4H,m),3.39-3.45(2H,m), 3.62-3.67(2H,m),4.11(2H,q,J=6.8Hz),4.99(2H,s),6.66(2H,d,J=8.7Hz),7.02(2H,d,J=8.7Hz), 7.60(1H,d,J=8.8Hz),7.82(1H,d,J=8.8Hz),7.86(1H,s),8.03(1H,d,J=8.3Hz),8.11(1H,d, J=8.3Hz),8.50(1H,s),9.22-9.37(4H,m),9.49-9.56(2H,s)
49	NMR(DMSO-d_6) δ :1.22(3H,t,J=7.3Hz),2.03-2.11(2H,m),3.00-3.15(4H,m),3.40-3.46(2H,m), 3.64-3.70(2H,m),4.11(2H,q,J=7.3Hz),4.22(2H,d,J=5.8Hz),5.62(2H,s),6.75(2H,d,J=9.3Hz), 6.98(2H,d,J=9.3Hz),7.14(1H,t,J=5.8Hz),7.71(1H,dd,J=1.4Hz,8.8Hz),7.81(1H,dd,J=1.4Hz, 8.8Hz),7.89(1H,s),8.01(1H,d,J=8.8Hz),8.11(1H,d,J=8.8Hz),8.45(1H,s),9.22-9.35(4H,m), 9.51(2H,s)

Table 20

Ex	DATA
50	NMR(DMSO-d_6) δ :2.02-2.10(2H,m),3.03-3.09(2H,m),3.11-3.18(2H,m),3.42-3.48(2H,m),3.64-3.71(2H,m),3.91(2H,s),5.06(2H,s),6.73(2H,d,J=8.8Hz),7.11(2H,d,J=8.8Hz),7.63(1H,dd,J=1.4Hz,8.3Hz),7.81(1H,dd,J=1.4Hz,8.3Hz),7.91(1H,s),8.03(1H,d,J=8.3Hz),8.12(1H,d,J=8.3Hz),8.49(1H,s),9.29(4H,br),9.53(2H,s)
51	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),2.04-2.16(1H,m),2.28-2.40(1H,m),2.71(1.5H,s),2.72(1.5H,s),2.99-3.09(2H,m),3.26-3.42(4H,m),3.62-3.76(2H,m),4.25(2H,q,J=7.2Hz),4.36(2H,s),5.02(2H,s),6.67(2H,d,J=8.4Hz),7.22(2H,d,J=8.4Hz),7.67(1H,d,J=8.4Hz),7.83(1H,d,J=8.4Hz),7.90(1H,s),8.03(1H,d,J=8.4Hz),8.10(1H,d,J=8.4Hz),8.51(1H,s),9.37(2H,s),9.56(2H,s),11.21(1H,s)
52	NMR(DMSO-d_6) δ :2.08-2.12(1H,m),2.29-2.41(1H,m),2.70(1.5H,s),2.72(1.5H,s),2.96-3.08(5H,m),3.25-3.42(4H,m),3.62-3.76(2H,m),5.00(2H,s),6.65(2H,d,J=8.8Hz),7.23(2H,d,J=8.8Hz),7.68(1H,dd,J=1.6Hz,8.4Hz),7.84(1H,d,J=8.0Hz),7.90(1H,s),8.01(1H,d,J=8.4Hz),8.09(1H,d,J=8.0Hz),8.54(1H,s),9.44(2H,s),9.61(2H,s),11.30(1H,s)
53	NMR(DMSO-d_6) δ :1.29(3H,t,J=7.2Hz),2.04-2.14(1H,m),2.29-2.40(1H,m),2.71(1.5H,s),2.73(1.5H,s),2.99-3.09(2H,m),3.28-3.40(4H,m),3.61-3.72(2H,m),4.24(2H,q,J=7.2Hz),5.14(2H,s),6.68(2H,d,J=8.8Hz),7.11(2H,d,J=8.8Hz),7.68(1H,dd,J=1.6Hz,8.8Hz),7.83(1H,dd,J=1.6Hz,8.4Hz),7.91(1H,s),8.03(1H,d,J=8.4Hz),8.10(1H,d,J=8.4Hz),8.49(1H,s),9.35(2H,s),9.55(2H,s),11.22(1H,s),11.41(1H,s)
54	NMR(DMSO-d_6) δ :2.04-2.12(1H,m),2.25-2.37(1H,m),2.71(1.5H,s),2.72(1.5H,s),2.97-3.07(2H,m),3.25-3.42(4H,m),3.60-3.72(2H,m),4.87(2H,s),5.30-5.85(2H,br),6.62(2H,d,J=8.8Hz),7.17(2H,d,J=8.8Hz),7.73(1H,dd,J=1.6Hz,8.8Hz),7.81(1H,dd,J=1.6Hz,8.8Hz),7.72(1H,s),7.99(1H,d,J=8.8Hz),8.08(1H,d,J=8.8Hz),8.45(1H,s),9.34(2H,s),9.54(2H,s),11.16(1H,s)
55	NMR(DMSO-d_6) δ :2.03-2.15(1H,m),2.28-2.38(1H,m),2.67(3H,s),2.71(3H,d,J=4.9Hz),2.97-3.11(2H,m),3.22-3.46(4H,m),3.60-3.75(2H,m),4.93(2H,s),6.62(2H,d,J=9.2Hz),7.17(2H,d,J=9.2Hz),7.67(1H,br d),7.82(1H,dd,J=1.8Hz,8.6Hz),7.90(1H,br s),8.00(1H,d,J=8.6Hz),8.08(1H,d,J=8.6Hz),8.48(1H,s),9.35(2H,s),9.55(2H,s),11.16(1H,br s)
56	NMR(DMSO-d_6) δ :2.02-2.16(1H,m),2.25-2.40(1H,m),2.71(3H,d,J=4.4Hz),2.78(6H,s),2.98-3.10(2H,m),3.24-3.48(4H,m),3.60-3.80(2H,m),5.00(2H,s),6.63(2H,d,J=8.8Hz),7.21(2H,d,J=8.8Hz),7.66(1H,dd,J=1.6Hz,8.4Hz),7.82(1H,dd,J=1.6Hz,8.4Hz),7.88(1H,br s),8.01(1H,d,J=8.4Hz),8.09(1H,d,J=8.4Hz),8.49(1H,s),9.34(2H,s),9.55(2H,s)
57	NMR(DMSO-d_6) δ :0.85-0.89(3H,m),1.23-1.30(5H,m),1.59-1.72(2H,m),2.06-2.13(1H,m),2.31-2.41(1H,m),2.95-3.05(4H,m),3.25-3.45(4H,m),3.68-3.73(2H,m),4.25(2H,q,J=7.2Hz),4.36(2H,s),5.02(2H,s),6.66(2H,d,J=8.8Hz),7.22(2H,d,J=8.8Hz),7.66(1H,dd,J=1.6Hz,8.8Hz),7.82(1H,dd,J=1.6Hz,8.8Hz),7.91(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.48(1H,s),9.28(2H,s),9.51(2H,s),10.88(1H,s)
58	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.6Hz),2.07-2.16(1H,m),2.39-2.49(1H,m),2.91-3.02(2H,m),3.24-3.42(4H,m),3.72-3.76(2H,m),4.22-4.34(4H,m),4.35(2H,s),5.02(2H,s),6.66(2H,d,J=8.8Hz),7.20(2H,d,J=8.8Hz),7.41-7.44(3H,m),7.61-7.68(3H,m),7.83(1H,dd,J=1.2Hz,8.8Hz),7.90(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.50(1H,s),9.34(2H,s),9.54(2H,s),11.41(1H,s)
59	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.78-1.83(2H,m),3.36-3.38(2H,m),3.44-3.49(2H,m),3.52-3.58(4H,m),4.24(2H,q,J=7.2Hz),4.38(2H,s),5.00(2H,s),6.69(2H,d,J=9.2Hz),7.18(2H,d,J=9.2Hz),7.37(4H,s),7.64(1H,dd,J=1.2Hz,8.4Hz),7.81(1H,dd,J=1.4Hz,8.8Hz),7.91(1H,s),8.03(1H,d,J=8.8Hz),8.11(1H,d,J=8.4Hz),8.47(1H,s),9.20(2H,s),9.47(2H,s)
60	NMR(DMSO-d_6) δ :1.15(3H,t,J=7.1Hz),1.73-1.83(2H,m),2.53-2.68(2H,m),2.68-2.86(2H,m),3.08(3H,s),3.29-3.41(6H,m),4.03(2H,br s),4.97(2H,s),6.58(2H,d,J=8.8Hz),7.16(2H,d,J=8.8Hz),7.66(1H,dd,J=1.5Hz,8.8Hz),7.79(1H,dd,J=1.5Hz,8.8Hz),7.92(1H,s),8.01(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.45(1H,s),9.18(2H,s),9.45(2H,s)

Table 21

Ex	DATA
61	NMR(DMSO-d_6) δ :1.79-1.85(2H,m),2.49-2.53(2H,m),2.65-2.69(2H,m),2.94(2H,s),3.08(3H,s), 3.36-3.39(2H,m),3.42-3.45(2H,m),4.96(2H,s),6.58(2H,d,J=9.0Hz),7.03(1H,s),7.13(1H,s), 7.15(2H,d,J=9.0Hz),7.64(1H,dd,J=1.5Hz,8.3Hz),7.79(1H,dd,J=1.5Hz,8.8Hz),7.88(1H,s), 7.99(1H,s),8.05(1H,s),8.39(1H,s),9.90(2H,br)
62	NMR(DMSO-d_6) δ :1.16(3H,t,J=7.4Hz),2.05-2.12(2H,m),3.08-3.24(4H,m),3.37(2H,s),3.63-3.68 (2H,m),3.92-3.96(2H,m),4.05(2H,q,J=7.4Hz),5.06(2H,s),6.91(1H,d,J=9.2Hz),7.57(1H,d,J= 9.2Hz),7.63(1H,dd,J=1.5Hz,8.8Hz),7.84(1H,dd,J=1.2Hz,8.8Hz),7.89(1H,s),7.91(1H,d,J=2.5 Hz),8.05(1H,d,J=8.8Hz),8.13(1H,d,J=8.8Hz),8.50(1H,s),9.37(2H,s),9.53(2H,s),9.58(2H,s)
63	NMR(DMSO-d_6) δ :1.19(3H,t,J=1.2Hz),2.04-2.11(2H,m),2.39(2H,t,J=6.4Hz),2.58(2H,t,J=6.4 Hz),3.10-3.20(4H,m),3.64-3.68(2H,m),3.91-3.95(2H,m),4.07(2H,q,J=7.2Hz),5.03(2H,s), (1H,d,J=8.0Hz),7.55-7.61(2H,m),7.83(1H,d,J=8.8Hz),7.87(1H,s),7.95(1H,d,J=2.8Hz),8.03 (1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz),8.49(1H,s),9.35(2H,s),9.45(2H,s),9.56(2H,s)
64	NMR(DMSO-d_6) δ :0.87(3H,t,J=7.2Hz),1.24-1.32(2H,m),1.48-1.54(2H,m),1.78-1.85(2H,m), 2.03(2H,s),2.26(1H,s),3.26(1.3H,s),3.28(0.7H,s),3.52-3.78(8H,m),3.99(2H,t,J=6.8Hz),5.02 (2H,s),6.70-6.73(2H,m),6.95-7.00(2H,m),7.60-7.64(1H,m),7.83-7.87(2H,m),8.02-8.06 (1H,m),8.13(1H,d,J=8.8Hz),8.49(0.3H,s),8.55(0.7H,s),8.73(0.7H,s),8.89(0.3H,s),9.41(2H,s) ,9.45(1H,s),9.60-9.62(2H,m)
65	NMR(DMSO-d_6) δ :1.14-1.17(6H,m),1.78-1.84(2H,m),2.03(1.8H,s),2.26(1.2H,s),3.22(1.3H,s), 3.24(0.7H,s),3.50-3.78(8H,m),4.82-4.89(1H,m),5.02(2H,s),6.69-6.75(2H,m),6.94-7.00 (2H,m),7.63(1H,d,J=8.8Hz),7.83-7.87(2H,m),8.03-8.06(1H,m),8.12(1H,d,J=8.8Hz),8.50 (0.4H,s),8.56(0.6H,s),8.75(0.6H,s),8.92(0.4H,s),9.43-9.48(3H,m),9.61-9.64(2H,m)
66	NMR(DMSO-d_6) δ :1.78-1.85(2H,m),2.04(2H,s),2.25(1H,s),3.04-3.07(2H,m),3.49-3.75(8H,m), 5.02(2H,s),6.69-6.73(2H,m),6.83(1H,s),6.99-7.04(2H,m),7.41(1H,s),7.61-7.65(1H,m),7.80-7.84(1H,m),7.92(0.7H,s),7.94(0.3H,s),8.01(1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz),8.46(0.3H,s),8.50(0.7H,s),8.67(0.7H,s),8.81(0.3H,s),9.34(2H,s),9.38-9.41(1H,m),9.55-9.57(2H,m)
67	NMR(DMSO-d_6) δ :0.96-1.00(3H,m),1.78-1.86(2H,m),2.04(2H,s),2.25(1H,s),3.00-3.07(4H,m), 3.43-3.56(4H,m),3.57-3.74(4H,m),5.01(2H,s),6.68-6.72(2H,m),6.98-7.03(2H,m),7.61-7.65 (1H,m),7.79-7.82(1H,m),7.88-7.92(2H,m),8.03(1H,d,J=8.8Hz),8.12(1H,d,J=8.7Hz),8.44 (0.3H,s),8.47(0.7H,s),8.61(0.7H,s),8.74(0.3H,s),9.25(2H,s),9.30-9.33(1H,m),9.53(2H,s)
68	NMR(DMSO-d_6) δ :0.78(1.2H,t,J=7.2Hz),0.84(1.8H,t,J=7.2Hz),0.95-1.00(3H,m),1.74-1.85 (2H,m),2.07(1.8H,s),2.25(1.2H,s),3.00-3.10(2H,m),3.17-3.27(4H,m),3.44-3.54(4H,m),3.56-3.74(4H,m),5.01(2H,s),6.65-6.71(2H,m),6.96-7.00(2H,m),7.67-7.72(1H,m),7.80-7.84(1H,m) ,7.89(0.6H,s),7.92(0.4H,s),8.02(0.6H,s),8.05(0.4H,s),8.11(0.6H,s),8.13(0.4H,s),8.43(0.4H,s),8.48(0.6H,s),8.66(0.6H,s),8.80(0.4H,s),9.29(2H,s),9.37-9.39(1H,m),9.53-9.55(2H,m)
69	NMR(DMSO-d_6) δ :1.15(3H,m),1.79-1.88(2H,m),2.03(2H,s),2.26(1H,s),3.48-3.61(4H,m), 3.65-3.78(4H,m),4.10(2H,q,J=6.9Hz),4.98(2H,s),6.65-6.72(2H,m),6.96-7.06(2H,m),7.59 (1H,d,J=8.8Hz),7.82(1H,dd,J=1.9Hz,8.8Hz),7.85(1H,s),8.03(1H,d,J=8.8Hz),8.11(1H,d, J=8.8Hz),8.52(1H,d,J=8.8Hz),8.63(0.7H,s),8.77(0.3H,s),9.30(3H,s),9.53(3H,s)
70	NMR(DMSO-d_6) δ :1.22(3H,t,J=7.3Hz),1.77-1.87(2H,m),2.06(0.7H,s),2.27(0.3H,s),3.46-3.79 (8H,m),4.11(2H,q,J=7.3Hz),4.23(2H,d,J=5.9Hz),5.60(2H,s),6.73-6.81(2H,m),6.93-7.00 (2H,m),7.09(0.7H,t,J=5.8Hz),7.15(0.3H,t,J=5.8Hz),7.70(1H,d,J=8.3Hz),7.80-7.85(1H,m), 7.83(1H,s),7.99-8.40(1H,m),8.11(1H,d,J=8.8Hz),8.47(0.3H,s),8.53(0.7H,s),8.70(0.7H,s), 8.80(0.3H,s),9.32(2H,s),9.41-9.46(1H,m),9.51-9.80(2H,m)
71	NMR(DMSO-d_6) δ :1.79-1.88(2H,m),2.05(2H,s),2.26(1H,s),3.49-3.79(8H,m),3.89(1.3H,s),3.91 (0.7H,s),5.05(2H,s),6.71-6.78(2H,m),7.05-7.12(2H,m),7.59-7.64(1H,m),7.80-7.85(1H,m), 7.91(1H,d,J=8.8Hz),8.03(1H,dd,J=1.4Hz,8.8Hz),8.12(1H,d,J=8.8Hz),8.51(0.3H,s),8.55 (0.7H,s),8.66(0.7H,s),8.81(0.3H,s),9.29-9.37(3H,m),9.53-9.58(2H,m)

Table 22

Ex	DATA
72	NMR(DMSO-d_6) δ :1.14-1.18(3H,m),1.78-1.86(2H,m),2.14(1.8H,s),2.27(1.2H,s),3.35(1.2H,s), 3.37(0.8H,s),3.56-3.61(2H,m),3.66-3.94(6H,m),4.01-4.07(2H,m),5.05(2H,s),6.89-6.95 (1H,m),7.50-7.53(1H,m),7.63(1H,d,J=8.4Hz),7.84-7.93(3H,m),8.04-8.08(1H,m),8.13 (1H,d,J=8.4Hz),8.52(0.4H,s),8.56(0.6H,s),8.84(0.6H,s),8.93(0.4H,s),9.44(2H,s),9.53-9.56 (1H,m),9.64(2H,s)
73	NMR(DMSO-d_6) δ :1.19(3H,t,J=6.8Hz),1.80-1.87(2H,m),2.13(1.8H,s),2.27(1.2H,s),2.33-2.41 (2H,m),2.55-2.61(2H,m),3.58-3.62(2H,m),3.68-3.95(6H,m),4.07(2H,q,J=6.8Hz),5.24(2H,s), 6.91-6.97(1H,m),7.51-7.61(2H,m),7.83-7.88(2H,m),7.93(1H,dd,J=2.4Hz,12.8Hz),8.04 (1H,dd,J=3.2Hz,8.8Hz),8.12(1H,d,J=8.8Hz),8.52(0.4H,s),8.55(0.6H,s),8.81(0.6H,s),8.90 (0.4H,s),9.42(2H,s),9.52(0.4H,s),9.56(0.6H,s),9.62(2H,s)
74	NMR(DMSO-d_6) δ :2.02-2.09(2H,m),3.01-3.09(2H,m),3.09-3.16(2H,m),3.40-3.45(2H,m),3.63-3.69(2H,m),4.18(2H,q,J=5.4Hz),5.62(2H,s),6.75(2H,d,J=8.7Hz),6.97-7.03(2H,m),7.69 (1H,d,J=8.7Hz),7.80(1H,d,J=8.7Hz),7.92(1H,s),8.01(1H,d,J=8.7Hz),8.10(1H,d,J=8.7Hz), 8.44(1H,s),9.11-9.19(4H,m),9.47(2H,s),12.53(1H,br)
75	NMR(DMSO-d_6) δ :1.78-1.88(2H,m),2.07(0.7H,s),2.26(0.3H,s),3.45-3.76(8H,s),4.18(2H,d,J=5.4Hz),5.60(2H,s),6.74-6.81(2H,m),6.94(1H,t,J=5.4Hz),6.95-7.02(2H,m),7.68(1H,d,J=8.3Hz),7.79-7.83(1H,m),7.92(1H,s),7.99-8.03(1H,m),8.11(1H,d,J=8.3Hz),8.45(0.3H,s),8.50 (0.7H,s),8.64(0.7H,s),8.76(0.3H,s),9.24(2H,s),9.34(1H,s),9.48-9.54(2H,m),12.56(1H,br)
76	NMR(DMSO-d_6) δ :2.73(3H,s),3.01-3.11(2H,m),3.31-3.33(6H,m),3.52-3.55(2H,m),4.23(2H,s), 5.02(2H,s),6.66(2H,d,J=8.8Hz),7.22(2H,d,J=8.8Hz),7.67(1H,d,J=8.8Hz),7.80(1H,dd, J=2.0Hz,8.8Hz),7.92(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.47(1H,s),9.20(2H,s), 9.47(2H,s),10.73(1H,s)
77	NMR(DMSO-d_6) δ :0.87(3H,t,J=7.4Hz),1.22-1.31(2H,m),1.59-1.71(2H,m),2.06-2.14(1H,m), 2.32-2.43(1H,m),2.95-3.05(4H,m),3.25-3.47(4H,m),3.69-3.74(2H,m),4.24(2H,s),5.02(2H,s), 6.66(2H,d,J=9.2Hz),7.22(2H,d,J=9.2Hz),7.67(1H,dd,J=1.2Hz,8.8Hz),7.82(1H,dd, J=1.2Hz,8.8Hz),7.91(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.49(1H,s),9.32(2H,s), 9.53(2H,s),10.96(1H,s)
78	NMR(DMSO-d_6) δ :2.08-2.16(1H,m),2.38-2.49(1H,m),2.92-3.02(2H,m),3.24-3.46(4H,m),3.72-3.77(2H,m),4.23(2H,s),4.25-4.35(2H,m),5.02(2H,s),6.65(2H,d,J=8.8Hz),7.21(2H,d,J=8.8Hz),7.41-7.44(3H,m),7.60-7.64(2H,m),7.67(1H,dd,J=1.5Hz,8.8Hz),7.82(1H,dd,J=1.2Hz,8.8Hz),7.90(1H,s),8.02(1H,d,J=8.8Hz),8.10(1H,d,J=8.8Hz),8.49(1H,s),9.32(2H,s),9.53(2H,s), 11.35(1H,s)
79	NMR(DMSO-d_6) δ :1.79-1.84(1H,m),3.35-3.39(2H,m),3.45-3.49(2H,m),3.52-3.55(2H,m),3.58-3.62(2H,m),4.26(2H,s),5.00(2H,s),6.70(2H,d,J=8.8Hz),7.19(2H,d,J=8.8Hz),7.51(4H,s),7.65 (1H,dd,J=1.0Hz,8.8Hz),7.83(1H,dd,J=0.9Hz,8.8Hz),7.91(1H,s),8.03(1H,d,J=8.8Hz),8.10 (1H,d,J=8.8Hz),8.51(1H,s),9.38(2H,s),9.56(2H,s)
80	NMR(DMSO-d_6) δ :1.98-2.05(2H,m),3.06-3.17(4H,m),3.54-3.58(2H,m),3.81-3.85(2H,m),4.33 (2H,s),5.03(2H,s),6.68(1H,d,J=9.2Hz),7.59(1H,dd,J=2.8Hz,9.2Hz),7.66-7.69(1H,m),7.79-7.82(1H,m),7.95(1H,s),8.02-8.05(2H,m),8.11(1H,d,J=8.4Hz),8.49(1H,s),9.09(2H,s),9.21 (2H,s),9.48(2H,s)
81	NMR(DMSO-d_6) δ :2.06-2.12(2H,m),3.12-3.22(4H,m),3.31(2H,s),3.66-3.70(2H,m),3.95-3.98 (2H,m),5.06(2H,s),7.01(1H,d,J=9.2Hz),7.62-7.66(2H,m),7.84(1H,dd,J=1.2Hz,8.4Hz),7.93-7.95(2H,m),8.05(1H,d,J=8.0Hz),8.13(1H,d,J=8.8Hz),8.50(1H,s),9.40(2H,s),9.60(4H,s)
82	NMR(DMSO-d_6) δ :1.79-1.86(2H,m),2.13(1.8H,s),2.27(1.2H,s),3.27(1.2H,s),3.28(0.8H,s),3.56-3.62(2H,m),3.68-3.92(6H,m),5.04(2H,s),6.88-6.94(1H,m),7.49-7.56(1H,m),7.63 (1H,d,J=8.4Hz),7.83-7.86(1H,m),7.90-7.94(2H,m),8.03-8.06(1H,m),8.13(1H,d,J=8.8Hz), 8.50(0.4H,s),8.54(0.6H,s),8.79(0.6H,s),8.88(0.4H,s),9.40(2H,s),9.48(1H,s),9.61(2H,s)

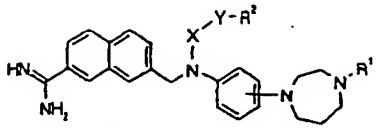
Table 23

Ex	DATA
83	NMR(DMSO-d_6) δ :2.06-2.12(2H,m),2.36(2H,t,J=6.4Hz),2.52(2H,t,J=6.4Hz),3.12-3.22(4H,m), 3.65-3.69(2H,m),3.93-3.97(2H,m),5.26(2H,s),6.97-7.02(1H,m),7.59-7.67(2H,m),7.83 (1H,dd,J=2.0Hz,8.8Hz),7.89(1H,s),7.96(1H,d,J=2.4Hz),8.02(1H,d,J=8.8Hz), 8.12(1H,d,J=8.8Hz),8.50(1H,s),9.38(2H,s),9.51(2H,s),9.58(2H,s)
84	NMR(DMSO-d_6) δ :1.81-1.87(2H,m),2.14(2H,s),2.28(1H,s),2.31-2.37(2H,m),2.51-2.55(2H,m), 3.59-3.63(2H,m),3.70-3.96(6H,m),5.03(2H,s),6.94-7.00(1H,m),7.55-7.61(2H,m),7.83-7.90 (2H,m),7.00(1H,dd,J=2.4Hz,12.0Hz),8.03(1H,d,J=8.8Hz),8.12(1H,d,J=8.8Hz),8.52(0.3H,s), 8.55(0.7H,s),8.82(0.7H,s),8.91(0.3H,s),9.44(2H,s),9.53(0.3H,s),9.57(0.7H,s),9.63(2H,s)
85	NMR(DMSO-d_6) δ :1.86-1.94(2H,m),2.81-2.84(2H,m),2.93-2.97(2H,m),3.09(3H,s),3.34-3.37 (4H,m),3.48-3.51(2H,m),4.97(2H,s),6.60(2H,d,J=9.0Hz),7.17(2H,d,J=9.0Hz),7.67 (1H,d,J=8.8Hz),7.79(1H,d,J=8.8Hz),7.91(1H,s),8.01(1H,d,J=8.8Hz),8.09(1H,d,J=8.8Hz), 8.46(1H,s),9.27(2H,s),9.46(2H,s)
86	NMR(DMSO-d_6) δ :0.96(6H,s),2.86-2.89(2H,m),3.09(3H,s),3.28-3.33(2H,m),3.35(2H,s),3.35 (2H,t,J=5.4Hz),4.99(2H,s),6.74(2H,d,J=8.8Hz),7.19(2H,d,J=8.8Hz),7.67(1H,dd,J=1.4Hz, 8.8Hz),7.83(1H,dd,J=1.9Hz,8.8Hz),7.91(1H,s),8.01(1H,d,J=8.8Hz),8.09(1H,d,J=8.8Hz), 8.51(1H,s),9.37(4H,s),9.56(2H,s)
87	NMR(DMSO-d_6) δ :0.89(3H,s),0.92(3H,s)2.25(1.5H,s),2.29(1.5H,s),3.09(3H,s),3.30(1H,s), 3.34(1H,s),3.43-3.54(4H,m),3.81-3.86(2H,m),4.99(2H,s),6.68(1H,d,J=9.2Hz),6.72 (1H,d,J=9.2Hz),7.16-7.21(2H,m),7.65-7.68(1H,m),7.84(1H,dd,J=1.6Hz,8.4Hz),7.90(1H,s), 8.01(1H,d,J=8.4Hz),8.09(1H,d,J=8.4Hz),8.52(1H,s),8.88(0.5H,s),8.91(0.5H,s),9.43-9.47 (3H,m),9.59(2H,s)
88	NMR(DMSO-d_6) δ :1.98-2.08(m,2H),3.07(s,3H),3.05-3.13(m,2H),3.15-3.22(m,2H),3.40-3.45 (m,2H),3.61-3.68(m,2H),4.99(s,2H),6.71(d,2H,J=8.8Hz),6.89(s,1H),7.20(d,2H,J=9.3Hz), 7.70(dd,1H,J=1.9Hz,8.8Hz),7.82(d,1H,J=8.8Hz),8.05(d,1H,J=1.5Hz),8.84-8.91(m,2H),8.95 (s,2H),9.25(s,2H)
89	NMR(DMSO-d_6) δ :1.80-1.89(m,2H),2.04(s,2H),2.26(s,1H),3.08(s,3H),3.48-3.58(m,4H),3.58-3.64(m,1H),3.65-3.78(m,3H),4.99(s,2H),6.72(d,0.6H,J=9.3Hz),6.74(d,1.4H,J=9.3Hz),6.86 (s,0.7H),6.88(s,0.3H),7.18(d,1.4H,J=8.8Hz),7.18(d,0.6H,J=8.9Hz),7.72(dd,1H,J=2.0Hz, 8.8Hz),7.82(d,1H,J=8.8Hz),8.08(d,0.3H,J=1.9Hz),8.11(d,0.7H,J=1.4Hz),8.62(s,0.7H),8.76 (s,0.3H),9.12(s,2H),9.26-9.32(m,1H),9.32-9.42(m,2H)
90	NMR(DMSO-d_6) δ :1.82-1.89(2H,m),3.42-3.46(2H,m),3.59-3.64(4H,m),3.83-3.87(2H,m),4.22 (2H,s),4.98(2H,s),6.69(2H,d,J=8.8Hz),7.03-7.09(2H,m),7.16(2H,m),7.60(1H,dd,J=1.6Hz, 8.4Hz),7.74(1H,dd,J=1.6Hz,8.4Hz),7.87(1H,s),8.00(1H,d,J=8.4Hz),8.09(1H,d,J=8.4Hz), 8.12-8.16(2H,m),8.38(1H,s),13.86(1H,s)
91	NMR(DMSO-d_6) δ :2.06-2.13(1H,m),2.28-2.42(1H,m),3.70(1.5H,s),2.72(1.5H,s),2.99-3.08 (2H,m),3.26-3.40(4H,m),3.62-3.76(2H,m),4.24(2H,s),5.02(2H,s),6.66(2H,d,J=9.2Hz),7.22 (2H,d,J=9.2Hz),7.66(1H,dd,J=1.6Hz,8.4Hz),7.73(1H,dd,J=1.6Hz,8.4Hz),7.89(1H,s),8.01 (1H,d,J=8.8Hz),8.08(1H,d,J=8.8Hz),8.38(1H,s),8.96-9.50(2H,br),11.24(1H,s)
92	NMR(DMSO-d_6) δ :1.98-2.05(2H,m),2.55(3H,s),2.89-3.00(4H,m),3.28-3.33(2H,m),3.52-3.55 (2H,m),3.64(3H,s),3.92(2H,s),5.01(2H,s),6.60(2H,d,J=8.8Hz),7.25(2H,d,J=8.8Hz),7.57 (1H,d,J=7.2Hz),7.81(1H,s),7.89-7.94(2H,m),8.00(1H,dd,J=2.0Hz,8.8Hz),8.51(1H,s),9.20 (2H,s)
93	NMR(DMSO-d_6) δ :2.00-2.10(2H,m),3.00-3.08(2H,m),3.08-3.16(2H,m),3.38-3.45(2H,m), 3.60-3.70(2H,m),4.24(2H,s),5.01(2H,s),6.68(2H,d,J=8.8Hz),7.21(2H,d,J=8.8Hz),7.65 (1H,dd,J=1.6Hz,8.8Hz),7.73(1H,dd,J=1.6Hz,8.8Hz),7.89(1H,s),8.01(1H,d,J=8.8Hz),8.08 (1H,d,J=8.8Hz),8.37(1H,s),9.33(4H,br),11.43(1H,br)
94	NMR(DMSO-d_6) δ :2.02-2.14(1H,m),2.25-2.35(1H,m),2.72(3H,d,J=4.9Hz),2.96-3.08(2H,m), 3.24-3.44(4H,m),3.59-3.74(2H,m),4.87(2H,s),6.62(2H,d,J=9.0Hz),7.18(2H,d,J=9.0Hz), 7.67-7.74(2H,m),7.91(1H,br s),7.98(1H,d,J=8.6Hz),8.07(1H,d,J=8.6Hz),8.33(1H,br s)

Table 24

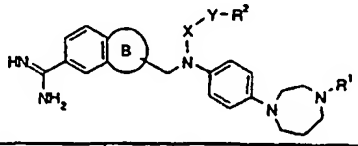
Ex	DATA
95	NMR(DMSO-d_6) δ :1.26(3H,t,J=6.8Hz),1.83-1.90(2H,m)3.33-3.37(2H,m),3.39-3.43(2H,m), 3.52-3.56(2H,m),3.62-3.66(2H,m),4.23(2H,q,J=6.8Hz),4.33(2H,s),4.93(2H,s),5.94(2H,s), 6.66(2H,d,J=9.2Hz),6.71(2H,d,J=6.4Hz),7.13(2H,d,J=9.2Hz),7.43(1H,dd,J=1.6Hz,8.8Hz), 7.69(1H,s),7.82-7.85(3H,m),8.06(2H,d,J=9.2Hz),8.13(1H,s),9.79(1H,s)
96	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.93-2.01(2H,m),2.42(3H,s),2.68-2.83(2H,m),2.95-3.03 (4H,m),3.50-3.53(2H,m),4.24(2H,q,J=7.2Hz),4.34(2H,s),4.95(2H,s),5.91(2H,s),6.61(2H,d, J=9.2Hz),7.16(2H,d,J=9.2Hz),7.46(1H,dd,J=1.6Hz,8.0Hz),7.71(1H,s),7.81-7.82(2H,m),7.85 (1H,d,J=8.0Hz),8.14(1H,s),9.77(1H,s)
97	NMR(DMSO-d_6) δ :1.27(3H,t,J=6.8Hz),2.00-2.04(2H,m),2.98-3.08(2H,m),3.08-3.17(2H,m), 3.38-3.45(2H,m),3.60-3.70(2H,m),4.24(2H,q,J=6.8Hz),4.36(2H,s),5.01(2H,s),6.69(2H,d,J= 8.8Hz),7.21(2H,d,J=8.8Hz),7.65(1H,dd,J=1.6Hz,8.8Hz),7.73(1H,dd,J=1.6Hz,8.8Hz),7.89 (1H,s),8.02(1H,d,J=8.8Hz),8.08(1H,d,J=8.8Hz),8.38(1H,s),9.37(4H,br),11.42(1H,br)
98	NMR(DMSO-d_6) δ :2.08-2.25(2H,m),2.67(3H,d),2.77(3H,d),3.00-3.15(2H,m),3.25-3.72(6H,m), 4.92(2H,s),6.62(2H,d),7.17(2H,d),7.28(1H,q),7.64(1H,d),7.71(1H,d),7.91(1H,s),7.97(1H,d), 8.04(1H,d),8.29(1H,s),10.45-10.60(1H,brs)
99	NMR(DMSO-d_6) δ :2.04-2.14(1H,m),2.22-2.34(1H,m),2.73(3H,d),2.78(3H,s),2.99-3.10(2H,m), 3.25-3.43(3H,m),3.56-3.92(3H,m),4.99(2H,s),6.63(2H,d),7.21(2H,d),7.65(1H,dd),7.72 (1H,dd),7.87(1H,s),8.00(1H,d),8.07(1H,d),8.85-9.35(1H,br),10.82-10.94(1H,brs),11.20-11.42(1H,brs)
100	NMR(DMSO-d_6) δ :2.04-2.12(1H,m),2.27-2.39(1H,m),2.71(1.5H,s),2.72(1.5H,s),2.98-3.08 (5H,m),3.23-3.42(4H,m),3.60-3.75(2H,m),4.58-4.88(2H,br),4.99(2H,s),6.65(2H,d,J=8.8Hz), 7.23(2H,d,J=8.8Hz),7.66(1H,dd,J=2.0Hz,8.4Hz),7.72(2H,dd,J=1.6Hz,8.4Hz),7.90(1H,s), 8.00(1H,d,J=8.8Hz),8.07(1H,d,J=8.8Hz),8.38(1H,s),11.09(1H,s)
101	NMR(DMSO-d_6) δ :1.24(3H,t,J=7.1Hz),1.93-2.03(2H,m),2.52-2.58(3H,m),2.88-3.05(6H,m), 3.10-3.20(2H,m),4.08(2H,d,J=7.1Hz),5.07(2H,s),5.90(2H,s),6.53(2H,d,J=8.8Hz),7.07(2H,d, J=8.8Hz),7.49(1H,dd,J=1.5Hz,8.3Hz),7.69(1H,br s),7.77-7.83(3H,m),8.09(1H,s),9.74(1H,s)
102	NMR(DMSO-d_6) δ :2.04-2.15(1H,m),2.27-2.40(1H,m),2.71(3H,d,J=4.8Hz),2.94-3.11(2H,m), 3.25-3.47(4H,m),3.60-3.75(2H,m),3.91(3H,s),4.88(2H,s),6.62(2H,d,J=9.2Hz),7.18(2H,d, J=9.2Hz),7.73-7.80(2H,m),7.96(1H,s),8.00(1H,d,J=7.6Hz),8.08(1H,d,J=7.6Hz),8.43(1H,s), 10.65(1H,brs),11.31(1H,brs),11.63(1H,brs)
103	NMR(DMSO-d_6) δ :1.27(3H,t,J=7.2Hz),1.85-1.93(2H,m),2.34(3H,s),2.52-2.75(2H,m),3.32-3.35(4H,m),3.45-3.49(2H,m),3.65(3H,s),4.24(2H,q,J=7.2Hz),4.35(2H,s),4.98(2H,s),6.60 (2H,d,J=8.8Hz),7.16(2H,d,J=8.8Hz),7.57(1H,dd,J=1.2Hz,8.8Hz),7.82(1H,s),7.92-7.95 (2H,m),8.01(1H,dd,J=1.6Hz,8.8Hz),8.52(1H,s),9.17(2H,s)
104	NMR(DMSO-d_6) δ :2.02-2.15(1H,m),2.30-2.40(1H,m),2.67(3H,s),2.71(3H,d,J=4.9Hz),2.98-3.10(2H,m),3.24-3.44(4H,m),3.60-3.75(2H,m),3.92(3H,s),4.94(2H,s),6.63(2H,d,J=9.0Hz), 7.18(2H,d,J=9.0Hz),7.69(1H,dd,J=1.6Hz,8.7Hz),7.78(1H,dd,J=1.6Hz,8.7Hz),7.93(1H,brs), 8.01(1H,d,J=8.3Hz),8.08(1H,d,J=8.3Hz),8.45(1H,brs),10.65(1H,s),11.34(1H,brs),11.65 (1H,s)
105	NMR(DMSO-d_6) δ :1.76-1.86(2H,m),2.19(3H,s),2.35-2.42(2H,m),2.75(3H,s),3.32(6H,s), 3.37-3.44(2H,m),3.64(4H,s),4.93(2H,s),6.55(2H,d,J=9.1Hz),7.12(2H,d,J=9.1Hz),7.47-7.59(1H,m),7.80(1H,brs),7.91-8.03(3H,m),8.51(1H,s),9.17(1H,brs)
106	NMR(DMSO-d_6) δ :2.04-2.15(2H,m),2.25-2.35(1H,m),2.73(3H,d,J=4.3Hz),3.02-3.10(2H,m), 3.04(3H,s),3.25-3.75(6H,m),3.91(3H,s),5.00(2H,s),6.65(2H,d,J=9.1Hz),7.23(2H,d,J=9.1Hz) ,7.69(1H,dd,J=1.5Hz,8.3Hz),7.78(1H,dd,J=1.5Hz,8.3Hz),7.78(1H,dd,J=1.5Hz,8.3Hz),7.94(1H,brs),8.02(1H,d,J=8.6Hz),8.08(1H,d,J=8.6Hz),8.46(1H,brs),10.16(1H,brs),10.91(1H,brs)
107	NMR(DMSO-d_6) δ :1.23(3H,t,J=7.1Hz),1.91(2H,brs),2.54(3H,s),2.65(2H,brs),2.84(2H,brs), 2.93(2H,brs),3.06(2H,brs),3.64(3H,s),4.04(2H,q,J=7.0Hz),5.10(2H,s),6.47(2H,d,J=8.8Hz), 7.07(2H,d,J=8.8Hz),7.62(1H,dd,J=1.2Hz,8.6Hz),7.79(1H,brs),7.87-7.99(3H,m),8.46 (1H,brs),9.16(1H,brs)

Table 25



Ex	R¹		X	Y	R²
108	-C(=NH)-Me		-SO_2-	-4-Ph-	-COOH
109	-Me		-SO_2-	-4-Ph-	-COOH
110	-C(=NH)-Me		-SO_2-	-4-Ph-	-COOEt
111	-C(=NH)-Me		-CO-	-4-Ph-	-COOH
112	-Me		-CO-	-4-Ph-	-COOH
113	-C(=NH)-Me		-SO_2-	-3-Ph-	-COOH
114	-Me		-SO_2-	-3-Ph-	-COOH
115	-C(=NH)-Me		-CO-	-3-Ph-	-COOH
116	-COOEt		-SO_2-	-CH_2-	-COOH
117	-$CONH_2$		-SO_2-	-CH_2-	-COOH
118	-CONHMe		-SO_2-	-CH_2-	-COOH
119	-$CON(Me)_2$		-SO_2-	-CH_2-	-COOH
120	-Me		-CO-	-CH_2-	-COOH
121	-Me		-CO-	-CH_2CH_2-	-COOH
122	-Me		-SO_2-	-CH_2-	-COOH
123	-Me		-SO_2-	-CH_2-	-COOEt
124	-Me		-SO_2-	-CH_2CH_2-	-COOH
125	-C(=HN)-Me		-CO-	-CH_2-	-COOH
126	-C(=HN)-Me		-CO-	-CH_2CH_2-	-COOH
127	-C(=HN)-Me		-SO_2-	-CH_2-	-COOH
128	-C(=HN)-Me		-SO_2-	-CH_2-	-COOEt
129	-C(=HN)-Me		-SO_2-	-CH_2CH_2-	-COOH

Table 26



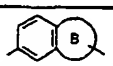
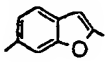
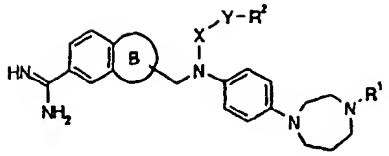
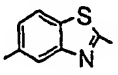
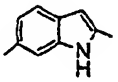
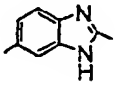
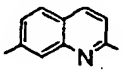
Ex		R¹	X	Y	R²
130		-Me	-CO-	-CH_2-	-COOH
131		-Me	-CO-	-CH_2CH_2-	-COOH
132		-Me	-SO_2-	-CH_2-	-COOH
133		-Me	-SO_2-	-CH_2-	-COOEt
134		-Me	-SO_2-	-CH_2CH_2-	-COOH
135		-C(=HN)-Me	-CO-	-CH_2-	-COOH
136		-C(=HN)-Me	-CO-	-CH_2CH_2-	-COOH
137		-C(=HN)-Me	-SO_2-	-CH_2-	-COOH
138		-C(=HN)-Me	-SO_2-	-CH_2-	-COOEt
139		-C(=HN)-Me	-SO_2-	-CH_2CH_2-	-COOH

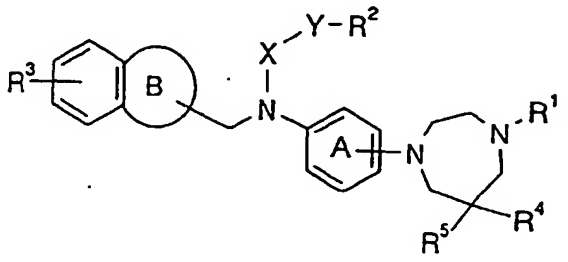
Table 27



Ex	B	R^1	X	Y	R^2
140		-Me	-CO-	$-CH_2-$	-COOH
141		-Me	-CO-	$-CH_2CH_2-$	-COOH
142		-Me	$-SO_2-$	$-CH_2-$	-COOH
143		-Me	$-SO_2-$	$-CH_2-$	-COOEt
144		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
145		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
146		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
147		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
148		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
149		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
150		-Me	-CO-	$-CH_2-$	-COOH
151		-Me	-CO-	$-CH_2CH_2-$	-COOH
152		-Me	$-SO_2-$	$-CH_2-$	-COOH
153		-Me	$-SO_2-$	$-CH_2-$	-COOEt
154		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
155		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
156		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
157		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
158		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
159		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
160		-Me	-CO-	$-CH_2-$	-COOH
161		-Me	-CO-	$-CH_2CH_2-$	-COOH
162		-Me	$-SO_2-$	$-CH_2-$	-COOH
163		-Me	$-SO_2-$	$-CH_2-$	-COOEt
164		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
165		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
166		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
167		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
168		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
169		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
170		-Me	-CO-	$-CH_2-$	-COOH
171		-Me	-CO-	$-CH_2CH_2-$	-COOH
172		-Me	$-SO_2-$	$-CH_2-$	-COOH
173		-Me	$-SO_2-$	$-CH_2-$	-COOEt
174		-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH
175		-C(=HN)-Me	-CO-	$-CH_2-$	-COOH
176		-C(=HN)-Me	-CO-	$-CH_2CH_2-$	-COOH
177		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOH
178		-C(=HN)-Me	$-SO_2-$	$-CH_2-$	-COOEt
179		-C(=HN)-Me	$-SO_2-$	$-CH_2CH_2-$	-COOH

Claims

1. A hexahydro-1,4-diazepine derivative represented by the following general formula (I) or its pharmaceutically acceptable salt:

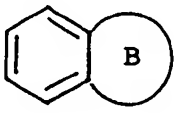


(I)

(wherein the symbols have the following meanings:

A: a phenylene or pyridylene group (which may be substituted),
B: forming a 5- or 6-membered aryl or heteroaryl,
X: a group of formula, -CO-, -CONH-, -CSNH-, - SO_2-, -SO_2NH-, or -SO_2N(-lower alkyl)-,
Y: a bond or a lower alkylene group,
R^1: a hydrogen atom, or a lower alkyl, -L-aryl, -L-heteroaryl, -L-COO-R^6, -L-CON(-R^6)-R^7, -C(=NH)-NH_2, or -C(=NH)-lower alkyl group,
R^2: a hydrogen atom, an -O-lower alkyl, -COOH, - COO-lower alkyl, -$CONH_2$, -CONH-lower alkyl, or -CON-di-lower alkyl group, or an aryl or heteroaryl group (which may be substituted),
R^3: an amidino group or a group capable of being converted into an amidino group in a living body,
R^4, R^5: a hydrogen atom or a lower alkyl group, which may be the same or different,
R^6, R^7: a hydrogen atom or a lower alkyl group, which may be the same or different, and
L: a bond or a lower alkylene group.)

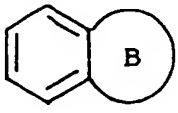
2. The hexahydro-1,4-diazepine derivative or its pharmaceutically acceptable salt as claimed in claim 1, wherein the ring



is naphthalene or benzofuran.

3. The hexahydro-1,4-diazepine derivative or its pharmaceutically acceptable salt as claimed in claim 2, wherein R^4 and R^5 are each a hydrogen atom.

4. The hexahydro-1,4-diazepine derivative or its pharmaceutically acceptable salt as claimed in claim 3, wherein the ring



is naphthalene; A is a phenylene group (the phenylene group may be substituted with a substituent selected from

a halogen atom, or an amino, cyano, nitro, -OH, -COOH, lower alkyl, -O-lower alkyl, or -COO-lower alkyl group), or a pyridylene group; and R^3 is an amidino group.

5. The hexahydro-1,4-diazepine derivative or its pharmaceutically acceptable salt as claimed in claim 4, wherein A is a phenylene or pyridylene group; X is a group of formula, -CO-, -CSNH-, $-SO_2-$, or $-SO_2NH-$; R^1 is a hydrogen atom, or a lower alkyl, pyridyl, or $-C(=NH)-CH_3$ group; and R^2 is a hydrogen atom or a -COOH, -COO-lower alkyl, or tetrazolyl group.

6.

N-[4-(4-Acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]acetamide,
ethyl [N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetate,
ethyl N-[N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]glycinate,
ethyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]malonamate,
[N-[6-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]acetic acid,
[N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl)-N-[(7-amidino-2-naphthyl)methyl)sulfamoyl]acetic acid,
N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]succinamic acid,
ethyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]malonamate,
ethyl N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]succinamate,
N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)phenyl]-N-[(7-amidino-2-naphthyl)methyl]thioamidoacetic acid,
N-[4-(4-acetimidoylhexahydro-1H-1,4-diazepin-1-yl)-3-pyridyl]-N-[(7-amidino-2-naphthyl)methyl]succinamic acid, or
pharmaceutically acceptable salts thereof.

7. A pharmaceutical composition containing the hexahydro-1,4-diazepine derivative or its pharmaceutically acceptable salt as claimed in claim 1 and a pharmaceutically acceptable carrier.

8. The pharmaceutical composition as claimed in claim 7, which is an activated blood coagulation factor X inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/03267

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07D243/08, C07D401/04, C07D405/12, A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07D243/08, C07D401/04, C07D405/12, A61K31/55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
EA	JP, 10-017549, A (Banyu Pharmaceutical Co., Ltd.), 20 January, 1998 (20. 01. 98) (Family: none)	1-8
A	WO, 94/02472, A1 (Taisho Pharmaceutical Co., Ltd.), 3 February, 1994 (03. 02. 94), Claims & EP, 649843, A1 & US, 5478945, A & AU, 9345135, A	1-8
A	JP, 5-208946, A (Daiichi Pharmaceutical Co., Ltd.), 20 August, 1993 (20. 08. 93), Refer to all references & EP, 540051, A1 & TW, 210998, A & CN, 1072677, A & US, 5576343, A	1-8
A	JP, 59-139357, A (Torii & Co., Ltd.), 10 August, 1984 (10. 08. 84), Refer to all references & DE, 3402628, A1 & GB, 2134901, A & FR, 2540118, A & US, 4634783, A	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October, 1998 (20. 10. 98)	27 October, 1998 (27. 10. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)